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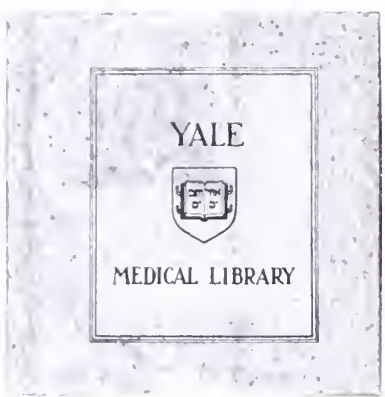
A METHODOLOGIC ANALYSIS OF RANDOMIZED CLINICAL TRIALS FOR MILD HYPERTENSION

PATRICK JAMES TOTH

1982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A METHODOLOGIC ANALYSIS OF RANDOMIZED CLINICAL TRIALS FOR MILD HYPERTENSION

by

Patrick James Toth

A thesis submitted to the
Yale University School of Medicine
in partial fulfillment of the requirements for
the degree of Doctor of Medicine
1982

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for my parents

ACKNOWLEDGEMENT

I am indebted to Ralph I. Horwitz for his patience and humor while guiding me through this project. Over the last four years he has become my valued teacher and friend.

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The issue of whether to treat all patients with mild hypertension (diastolic blood pressure = 90-110 mmHg) remains controversial despite the results of eight large-scale randomized clinical trials (RCTs). The most common medical problem in the adult population, mild hypertension contributes significantly to cardiovascular and therefore overall morbidity and mortality. The status of mild hypertension as one of the larger problems in clinical therapy has prompted much comment on the as yet unresolved dilemma of treatment. The purpose of this thesis will be not only to explain how this controversy has come to exist, but also to determine whether a methodologic analysis of the data can help to resolve the dispute. In the introduction of this paper, I shall develop an historical framework of investigations determining the therapeutic efficacy of pharmacologic intervention in hypertensive disease, progressing from the more severe to the less severe forms of this disorder. Investigations studying milder forms of hypertension encountered substantial scientific challenges, not encountered in studies of severe hypertension, requiring the design and implementation of large multi-center randomized trials. In the latter part of the introduction, I shall comment on the advantages of randomized clinical trials over observational studies, and conclude with a discussion of many of the issues involved in assessing the quality of an RCT (internal validity) and determining its applicability to clinical practice (external generalizability).

INTRODUCTION

Despite the association of hypertension with cardiovascular disease, it was not until the introduction of ganglionic blocking agents by Paton and Zamais (1) in 1949 that investigators could determine whether pharmacologic reduction of arterial blood pressure would reduce the risk of developing cardiovascular complications. The earliest studies dealt with "malignant" (accelerated) hypertension. The untreated clinical course of this disease is well-characterized and highly uniform: 80-90% of patients die within the first year of presentation (2). Death is secondary to arteriolar damage and generally results from renal failure due to nephrosclerosis, though intracerebral hemorrhage and congestive heart failure are also common. In 1952, McMichael (3) demonstrated immediate "benefit from treatment" with hexamethonium in 4 of 7 patients with malignant hypertension. Unfortunately, further information as to outcome was not provided, and thus it is difficult to evaluate therapeutic efficacy. In addition, therapy was complicated by the need for subcutaneous administration, difficulties titrating the drug, and severe side effects. Among the reported side effects were postural hypotension, urinary retention, constipation, tremor, visual disturbances, and confusion. With the development of better oral ganglionic blocking agents, and with the addition of hydralazine and reserpine, several investigators in the late 1950s reported significant reductions in short and long term morbidity among their treated patients

with accelerated hypertension (4,5,6,7). Similar studies were performed for "pre-malignant" (severe) hypertension. In addition to having markedly elevated blood pressures, all of these patients had evidence of serious end-organ disease (cardiac, renal, optic, central nervous system) by history, physical exam, or diagnostic tests. None of the patients had papilledema, hypertensive encephalopathy, or rapidly deteriorating renal function, and most of the patients had diastolic blood pressures lower than patients with accelerated hypertension. In these studies, patients treated with anti-hypertensive therapy had a substantial reduction in morbidity during the 4-7 years of follow-up (8,9). All of these studies included small numbers of treated patients (range: 7-84), and none of the studies employed a concurrent, untreated control group. Rather, the patients' survival was compared to the known natural course of the disease. Despite the small size and inadequate design of these studies, the results were quickly embraced by clinicians because of the remarkable potential benefits which had been previously unattainable.

These more severe forms of hypertension were relatively easily defined; the patients were all at high risk with most patients following a rapid and relentless downhill course. Hence, any improvement with pharmacologic therapy was readily appreciated. As investigators turned to the study of unaccelerated ("benign") essential hypertension, the problems of demonstrating the effectiveness

of therapy increased substantially. Though these patients were at some increased risk for developing cardiovascular disease, the risk of developing cardiovascular disease was highly variable and complications progressed slowly if at all. Since the outcome of an individual patient for a given period of observation was no longer predictable, the benefits of therapy could only be measured by comparing the incidence of death and morbid events in a treated population of hypertensive patients to that of a concurrently untreated by otherwise similar population of patients. The earliest studies, which were retrospective observational studies, proved to be inconclusive. In 1959, Leishman (10) reported his findings from a retrospective study of 402 patients who had been diagnosed as being hypertensive (diastolic blood pressure > 120 mmHg). At the discretion of their personal physicians, these patients with "benign" hypertension had either been started on pharmacologic therapy or been given no treatment at all. The period of time from the time of diagnosis ranged from 1 to 13 years. Leishman found a significant difference in mortality between these two groups of patients with nearly three times as many deaths in the group of patients not receiving medical therapy. However, in a similar study, Perrera (11) compared the mortality rate in 29 matched pairs of patients with "benign" hypertension (diastolic pressure > 120 mmHg) and found no difference between those patients who had not received treatment and those who had. There were 16 deaths in each group.

Feeling that observational studies were inadequate to assess properly the therapeutic efficacy of anti-hypertensive agents in unaccelerated hypertension, the Veterans Administration Cooperative Group (12) initiated a prospective randomized clinical trial in 1963. This study of 143 patients with "moderate" hypertension (diastolic blood pressure = 115-129 mmHg) was terminated early in 1967, after only four years of follow-up, when highly significant results led investigators to conclude that it was unethical to continue the trial. There were 27 morbid events including 4 deaths in the placebo group (39%) compared with 2 morbid events with no deaths in the actively treated group (3%). Morbid events included: aortic aneurysm, cerebral hemorrhage or thrombosis, retinopathy with or without papilledema, doubling of the Blood Urea Nitrogen $\left(> \frac{60\,mg}{100\,cc}\right)$ persistent elevation of the diastolic blood pressure (> 140 mmHg), congestive heart failure, and myocardial infarction. These results were consistent with the statistically significant findings of two other, smaller, prospective randomized clinical trials in patients with a similar severity of hypertension (diastolic blood pressure > 120 mmHg) (13,14).

By this time, data from the Framingham Heart Survey (15) had suggested that people with mild hypertension (diastolic blood pressure = 90-115 mmHg) are at increased risk for developing cardiovascular disease. The Framingham Study suggested not only that hypertensives are at increased risk of cardiovascular-related

morbidity and mortality, but also that the degree of risk is directly related to the systolic and diastolic pressures. This study, an epidemiologic investigation started in 1948, has followed over 5,000 adults biennially. Patients in the study are examined regularly for the development of cardiovascular disease as manifested by: coronary artery disease, myocardial infarction, congestive heart failure, cerebrovascular accident, claudication, sudden death, cardiovascular-related death, and death from all causes. Among the potential risk factors assessed in the study were: hypertension, serum cholesterol level, serum phospholipid level, relative body weight, smoking history, gender, race, and age. The investigators correlated the occurrence of cardiovascular events with the full range of diastolic and systolic pressures and as expected, the highest incidence of disease was in the hypertensive group (a diastolic pressure > 95 mmHg and a systolic pressure > 160 mmHg). However, this increased risk was found to extend to some degree over the full range of diastolic and systolic pressures. The risk was greater in men than women at all levels of blood pressure and increased in both groups with increasing age.

The dramatic benefits noted in the randomized clinical trials of moderate hypertension (diastolic blood pressure = 115-129 mmHg) led many physicians to believe that the benefits of anti-hypertensive therapy might extend to mild hypertension, and several studies have been performed in this group of patients. However, these large

prospective trials have had difficulties in administration, interpretation, and clinical application. Although patients with mild hypertension appear to be at some increased risk for developing cardiovascular disease, before attempting to treat all such patients it is imperative that we determine whether:

(1) Pharmacologic intervention will indeed result in a significantly decreased risk for developing cardiovascular disease.

Inherent in the mild hypertension trials is the assumption that pharmacologic lowering of the arterial blood pressure to "normotensive" levels will eliminate or at least diminish the relative risks associated with the disorder and that the difference resulting from the compared treatments will be clinically substantial. It is not sufficient for these studies to look only at proportional risk reduction. For deciding issues in personal health care, the absolute risk reduction to be gained by treatment is also significant. For example, if treatment for a given disorder resulted in a proportional risk reduction of 50%, this might mean that the chances of suffering a morbid event were reduced from one in 10,000 to one in 20,000, or it might mean that they were reduced from one in 10 to one in 20. When deciding whether treatment is indicated for each individual patient, the practicing physician must consider not just the proportional risk reduction, but the changes in absolute risks as well.

(2) The benefits of therapy will outweigh the hazards, inconvenience and expense.

A second assumption investigators have made is that treatment with anti-hypertensive agents is virtually benign though there is remarkably little information, particularly quantitative data, on the incidence of adverse effects associated with anti-hypertensive therapy. Even the information concerning the short term side-effects of anti-hypertensive medications is largely descriptive and falls into 3 major categories: fluid and electrolyte abnormalities (e.g., postural hypotension, hypokalemia, hyperuricemia); cardiac and vasomotor dysfunction (e.g., congestive heart failure); and disturbances of the central nervous system (fatigue, depression, impotence). When one considers the more subtle adverse effects that might be associated with chronic therapy such as diminished functional capacity(e.g., beta-blocking agents), poorer quality of life, and long-range side-effects, the available information is largely of an anecdotal nature and is not adequate for use in clinical decision-making.

(3) Risk factors other than level of blood pressure are equally or more important indicators for deciding who should and should not receive treatment.

Diastolic blood pressure, a relatively simple value to determine, provides useful information particularly in the asymptomatic patient. It is tempting to use this physical finding as a marker

by which all patients can be conveniently classified as either "normotensive" (those not requiring treatment) or "hypertensive" (those requiring treatment). But this is not enough, for such an approach fails to do justice to the complexity of the problem. Co-morbid clinical characteristics (such as age, gender, race, smoking, diabetes mellitus, and evidence of end-organ disease) are relevant to the development of cardiovascular disease and so must be taken into consideration when weighing issues of personal health. A study which fails to do so is incomplete and fails to provide the practicing physician with the information needed to make specific decisions for individual patients.

The treatment question is made even more compelling by data from the National Health Survey of people in the United States between 18 to 74 years of age, which estimates that approximately 26% of the adult population has a diastolic pressure greater than 90 mmHg. Of people 45 years of age and older, approximately 35% of men and 29% of women have "mild hypertension" (diastolic blood pressure = 90-110 mmHg). Additionally, there is another 35% of the population with a diastolic pressure of 80-89 mmHg (16).

Recognizing the importance of the problem, several groups of investigators performed studies to determine whether anti-hypertensive therapy is efficacious in mildly hypertensive patients. Many research strategies were available, but most researchers chose to employ prospective randomized clinical trials. Observational cohort studies

were generally considered to be inadequate to study this complex problem as such studies permit substantial bias (17,18). Since a crucial part of the assessment of therapeutic efficacy is the choice of the research strategy, I will now discuss why the RCT has come to be the accepted scientific "gold standard".

Randomized clinical trials have an advantage over observational surveys in that they employ several experimental principles which help to minimize the occurrence of bias (19). The chief advantage of the RCT is the process of randomization, a method by which patients who have met admission criteria can be entered into a study and assigned treatment in a purely random manner. In clinical practice, the choice of therapy is determined by both the physician and the patient. These preferences can introduce serious selection bias into a study however, by assigning patients with a particularly good (or poor) prognosis to one treatment modality or the other. The randomization process helps to ensure that patients in the experimental group are prognostically equivalent to those in the compared group. There are several other important scientific principles intrinsic to the design of the RCT which must be mentioned. Two of the principles involve the establishment of criteria to exclude either patients with strong indications or contraindications to any of the treatments being studied or patients who are so ill that death occurs before randomization can take place. Two other principles are concerned with the analysis of data. Patients who later change their

randomized treatment (e.g., patients with mild hypertension receiving placebos who are later switched to active anti-hypertensive medications because their blood pressure rises above pre-defined limits) can either be eliminated or, preferably, considered separately in the analysis. Lastly, the patients can be stratified according to pertinent pre-treatment characteristics so that the effects of treatment can be assessed separately among prognostically similar groups of patients. At the same time, stratification helps to compensate for any pre-treatment prognostic disparities that may have occurred in spite of the randomization process (20).

The prospective randomized clinical trial is a method which has been developed to find answers to clinical questions while adhering to scientific experimental principles. A well-designed RCT must meet several requirements in each of three major areas: the establishment of the baseline state, the performance of the maneuver (the treatment phase), and the detection and analysis of outcome events (21,22).

The Baseline State

The investigators' first responsibility is to define precisely the disease in question by providing the diagnostic criteria used (e.g., the Veterans Administration Cooperative Study defined mild hypertension as a diastolic blood pressure range of 90-114 mmHg) (23). The population of patients which is entered into the study

must be described with particular attention given to not only the severity of the disease under study but also co-morbid risk factors that might influence outcome. This relevant information should be collected so that it will be available to stratify the patients into prognostic subgroups when it is time to analyze the data.

Having fully described the study population, investigators must then ensure that the patients assigned to each of the compared treatments are at equal risk for developing outcome events. Ideally, the patients should be identical except for the therapeutic maneuver under study; since this is obviously not possible, random assignment of treatment is necessary to prevent selection bias. This process should be both blinded and strictly random. The assignment of treatment is not truly random if patients are assigned treatment by alternating: days of the week, admitted patients, admitting physicians, admitting hospital wards, etc. A physician could knowingly or unknowingly bias the results by withholding patients with a particularly poor (or good) prognosis until the "right" time when they would receive what the admitting physician considered the more desirable therapy (24). In addition, delays in the administration of treatment could in and of themselves influence the results. Though there are reported instances of physicians deliberately attempting to select specific treatments for some of their patients (24), the main goal of blinded random allocation is to prevent unintended bias from entering into studies. The efficacy

of the randomization process should then be confirmed by examining the distribution of patients in the compared populations (22,25).

Execution of the Therapeutic Maneuver

Again, the first requirement is that the investigators define the compared treatments. The definitions should include a complete discussion of the experimental therapy as well as the compared treatment (23) (e.g., no treatment, type of placebo, etc.). Additionally, all ancillary therapy should be described and particular emphasis should be given if it differs among the compared treatments, e.g., advice given to patients with mild hypertension regarding diet, smoking, exercise, and weight reduction (26). These co-maneuvers should be identical in the compared groups to prevent confusion when the results of the trial are later examined. The maneuver should be performed with an appropriate and equal level of skill (23). However, opinions can vary as to what is "appropriate". There has been much debate over whether treatment should be administered in such a way as to approximate common clinical practice or whether it should be administered in the best possible fashion. This dispute has been at issue in several studies, for example, those comparing the medical and surgical management of coronary artery disease (27,28).

Regardless of whether treatment is deemed to be "appropriate", it must be administered with equal rigor. When possible, patients should be blinded as to the type of treatment they are receiving.

This is particularly important for the monitoring of the more subjective outcome events and adverse effects (22,23). The physicians should also be blinded. Since drug therapy requires regulation, studies must be designed to allow for "stepped" care so that dosage can be individualized. The results of the UGDP study on diabetes mellitus have been questioned because oral hypoglycemic agents were given in a fixed dosage to all patients with no attempt to regulate the blood glucose level (29). Similarly, a study on mild hypertension would be seriously flawed if the same anti-hypertensive medication were given in the same dose to all patients with no attempt to adjust treatment to the measured blood pressure. A drug regimen must be allowed to achieve its designed physiologic effect for it to have any chance of influencing outcome (23). Hence, in addition to providing "stepped care", the investigators should assess compliance with the chief therapeutic maneuver and all co-maneuvers.

Detection and Analysis of Outcome Events

The events chosen as the main outcome of an RCT must be suitably selected so that they are both clinically relevant and statistically countable (21); the range of events should encompass not only benefits of therapy but also possible adverse effects (23). This is not always easy however. If some of the chief effects of treatment consist of subtle alterations in symptoms or functional capacity, or subjective changes in quality of life, it may be

difficult to quantify these data so that they can be statistically analyzed. The selection of outcome events is particularly important in the mild hypertension trials as these patients are generally healthy symptomless patients who are at low risk for dying or suffering morbid events such as myocardial infarction, cerebrovascular accident, or congestive heart failure (30). Failure to respond to assigned therapy should not necessarily be considered a trial end point. Patients in the mild hypertension studies who were removed from the trials because their diastolic pressure continued to rise above the range for mild hypertension defined within the studies should not be considered as having had an outcome event regardless of their assigned treatment. Following the selection of outcome events, there must then be equal detection of end points in the patients receiving the compared treatments. All trial end points should then be reviewed by an independently blinded committee (22).

The patients in each of the treatment populations should be stratified into prognostic subgroups according to clinical features which are relevant to the outcome events that have been selected. In the mild hypertension trials, pertinent clinical data might include such risk factors as the degree of diastolic pressure elevation, duration of pressure elevation, the presence of diabetes mellitus, a history of smoking, and evidence of end-organ disease by history, physical exam, or diagnostic tests (31). The results

of the therapeutic maneuver should then be presented for each of the prognostic strata rather than the study population as a whole. This will achieve a more effective and clinically meaningful comparison of the benefits of treatment for patients at variable degrees of risk. Those patients lost to follow-up or withdrawn from the study must be included in the final analysis of data. They should be fully described, and the reason for their removal from the study documented (patient vs. investigator initiated). If there is a significant difference between the compared regimens in the number of patients who have left or been removed from a study, a reason should be sought; in any case, if the overall dropout rate exceeds 15% or the dropout rate is greater than the incidence of outcome event, the results of the study may be unreliable (22,23).

The extrapolation of the results of any study concerned with clinical therapy is an inevitable problem, distinct from issues involved with assessing internal validity. If the patients in the study do not suitably represent the eligible population, then the reader may reject any subsequent findings as being irrelevant to the patients that he/she sees in clinical practice (32). Investigators should provide evidence for having estimated the size of the trial population necessary to demonstrate a statistically significant difference (at a stated level of significance, e.g., $\alpha = .05$) between the compared treatments for the selected

outcome events. A description of population transfers should follow, beginning with an explanation of the manner in which the target population was identified and screened. The overall yield from the number of people screened to the number of patients eventually admitted into the trial should be included. A complete description of both the admission and rejection criteria should be provided so that the reader can obtain a clear picture of the patients studied in the trial. Lastly, a description of the eligible patients not entered into the trial should be included with specific reasons for their ineligibility (e.g., poor motivation).

METHODS

I have used several criteria for selecting papers for review in this thesis. The study had to be a prospective randomized clinical trial concerned with determining the efficacy of treatment in reducing morbidity and mortality in patients with mild hypertension. To facilitate the review, I have selected only those investigations which have been published in the English language literature. A computer-assisted search of the literature was performed identifying 86 potentially relevant articles published between 1968-1981. These included 13 (33-45) papers on 11 large-scale RCTs of mild hypertension, only eight (33-43) of which have been completed (see Table 1). Of the three incomplete trials, one, the Medical Research Council (MRC) (44) study in Great Britain, and a second, the European Working Party on Hypertension in the

Elderly (EWPHE) (45) study are ongoing trials. However, due primarily to problems with funding the project, the full-scale Veterans Administration-National Heart, Lung, and Blood Institute (VA-NHLBI) study was never implemented after the two-year feasibility trial was completed. Pertinent preliminary studies (46-52), editorials, letters, and policy statements (30,53-63) accounted for 20 of the articles identified in the computer search. In addition, material cited in the reports of the RCTs has been collected and reviewed. Dr. H. Mitchell Perry of the VA-NHCBI group (64) and Dr. Edward Frohlich of the Hypertension Detection and Follow-up Program (65) were contacted in an effort to add any published or, as yet, unpublished data which might be of importance to this review. The vast majority of papers identified by the computer search (53) were not suitable for this review, since these studies compared the pressure-lowering capacity of various drug regimens in mildly hypertensive patients.

To evaluate the eight completed studies, I have developed a broad set of methodologic criteria for each of the three major areas critical to the design of an RCT. I will now present the methodologic standards and the operational criteria which I have developed to ensure that these methodologic standards are fulfilled. The purpose of applying these criteria to each of the trials is to ensure that the results are at the same time scientifically valid and clinically meaningful.

The methodologic standard and the criteria necessary to fulfill the standard are arranged in tabular form on the following pages.

A. Establishment of the Baseline State

Methodologic Standard	Criteria to Fulfill Methodologic Standard
1. The patients admitted into the trial suitably represent the eligible population.	Method of identifying the target population. Method of screening the target population. Precise statement of admission criteria (e.g., defined blood pressure range of mild hypertension). Precise statement of rejection criteria (e.g., evidence of severe hypertensive complications, unrelated terminal illness, poorly motivated patients). Description of eligible patients not entered into the study. Determination of the overall yield of randomized patients from the screened population.

2. The study population is thoroughly described for clinical and demographic characteristics.	Attention to grading the severity of the disease (e.g. establishing subgroupings within the defined range for mild hypertension on the basis of diastolic blood pressure establishing subgroupings on the basis of evidence of end-organ disease). Consideration of comorbid risk factors including demographic data (e.g., age; gender; history of smoking; evidence for hyperlipidemia; history of diabetes mellitus).
3. The patients receiving the compared treatments are at equal risk for developing outcome events.	Allocation of treatment in a random double-blinded fashion. Confirmation of the efficacy of this process by comparing the post-randomization distribution of patients.

B. Execution of the Therapeutic Maneuver

1. The compared treatment regimens are fully delineated.	Precise statement of the primary experimental maneuver (e.g., type of medication, dosage schedule, goal of treatment [desired blood pressure range]). Precise statement of the compared treatment (e.g., characteristics of the placebo). Description of all prescribed ancillary therapy (e.g., dietary restrictions, advice concerning smoking)
2. The compared treatments are applied with similar proficiency	Double-blind administration of treatment Monitoring for compliance of with the assigned regimen and all prescribed co-maneuvers (e.g., pill counts).

Monitoring for outside co-interventions.

Provision for "stepped care" so that the administration of treatment can be individualized according to the measured blood pressure.

Provision for instituting active therapy for those patients whose blood pressure exceeds the upper limit for mild hypertension (as defined in that particular study).

C. Detection and Analysis of Outcome Events

1. The range of trial end points selected is clinically relevant and statistically countable.

Comparison of fatality rates.

Comparison of the incidence of major as well as minor morbid events.

Equally rigorous comparison of side effects of treatment including subtle changes in functional capacity and quality of life.

	Plans for follow-up of possible long-range adverse effects associated with chronic therapy.
2. There is equal detection of outcome events.	Well-circumscribed diagnostic criteria established for each trial end point and applied to all patients (e.g., myocardial infarction might require electrocardiographic changes and an elevation of serum cardiac enzymes),
	Review of all end points by an independent blinded committee.
	Prognostic stratification to detect benefits/hazards of treatment in patients at varying degrees of risk.

Similar surveillance and diagnostic procedures for the compared groups.

Comparison of the incidence of dropouts/withdrawals.

I have appraised each of the 8 completed studies (Table 1) to determine the degree to which each of these methodologic standards has been fulfilled. Though I have presented this exhaustive list of methodologic standards, in the review of each individual study I will focus on those standards which contribute most to understanding the deficiencies in experimental design which may have influenced the subsequent results.

In an effort to examine all of the results in a standardized fashion, I have developed a list of outcome events which will be applied to each of the studies:

(1) Death from all causes

(2) Major morbid events: myocardial infarction, cerebrovascular accident, congestive heart failure, dissecting aortic aneurysm.

(3) Minor morbid events: left ventricular hypertrophy, evidence of renal failure, retinopathy, transient ischemic attacks.

(4) Adverse effects: biochemical as well as physiologic, subjective changes in functional capacity and quality of life.

While one can debate the "appropriateness" of any list of outcome events, I maintain that this systematic approach to evaluating the results of these many trials can provide useful information in terms of assessing the efficacy of anti-hypertensive therapy in preventing various types of outcome in this heterogeneous, low-risk population.

RESULTS

VETERANS ADMINISTRATION COOPERATIVE GROUP (33-35)

Summary

This trial was designed to determine whether anti-hypertensive therapy reduces cardiovascular-related morbidity in mildly hypertensive patients. In this study, the number of patients screened was not stated. Patients were selected from a hospitalized population; those with an average diastolic blood pressure of 90-114 mmHg on the fourth through sixth hospital day were eligible for admission to the study. Patients were excluded from the study on the basis of: 1) evidence of complications of severe hypertension, e.g., hypertensive encephalopathy, cerebrovascular hemorrhage; 2) surgically treatable hypertension; 3) unrelated terminal illness; 4) a demonstrated unwillingness to comply with assigned therapy. The investigators decided not to exclude all patients with end organ complications, since this would have restricted the size of the trial population, and more importantly, would have severely limited the general applicability of the results. Consequently, 58% of the 380 participants admitted to the trial had evidence of end organ disease. Additional characteristics of the study population are provided in Table 2. Whereas 186 subjects were randomized to receive the experimental regimen (see Table 3), 194 were randomized to the placebo group. The mean duration of follow-up was 3.3 years. A mean difference

in diastolic pressure of 18.6 mmHg was achieved between the compared groups in this study; this was the largest difference exhibited in any of the RCTs. Patients were allowed to continue in this trial untreated until their diastolic blood pressure exceeded 124 mmHg on three consecutive visits. At such time, patients were designated as "treatment failures" and known active medication was administered. There were 20 such treatment failures during the trial, all from the control group (10%).

All trial end-points were reviewed by a blinded committee. There were 10 deaths (5.4%) in the actively treated group and 21 deaths (10.8%) in the placebo group (see Table 5). The incidence of major events (myocardial infarction, congestive heart failure, cerebrovascular accident) was 4.8% in the treated group as compared with 14.8% in the placebo group (see Table 6). The data for minor end-points was incomplete. In addition to comparing the incidence of trial end-points between the treated and untreated groups, the investigators examined the rate of trial end-points and the effectiveness of treatment with respect to risk factors present at entry: cardiovascular-renal abnormalities (the prevalence of which was higher than in the general population of mildly hypertensive patients), degree of diastolic blood pressure elevation, and age. The majority of patients developing morbid events were in the older age group. There was nearly a three to one predilection for suffering a morbid event in those patients over 50 years of age

regardless of the assigned treatment. The presence of prior cardiovascular damage greatly increased the risk for developing morbid events following randomization. The level of pre-randomization diastolic blood pressure was also found to contribute to the rate of trial end points. The effectiveness of treatment was evident in those patients with a pre-randomization diastolic blood pressure greater than 104 mmHg. The incidence of outcome events was 32% (35) in the treated group as compared with 8% (8) in the placebo group. However, the difference in the incidence of outcome events between treated and placebo patients was less clearcut in those subjects with a pre-randomization diastolic pressure below this level (treated: placebo = 16% [14 outcome events]: 25% [21 outcome events]). Indeed, these patients seemed to derive little benefit from treatment unless they had cardiovascular abnormalities at entry or were over 50 years of age.

Over 40% of the patients in the treated group experienced hypotensive side effects shortly after starting treatment. The authors attributed this high incidence to the fact that the protocol called for all patients assigned to the group to begin treatment with a triple-drug regimen rather than a single antihypertensive agent. Two treated patients were removed from the trial because they developed reactions presumed to be due to drug toxicity. In addition, 29 patients (control: treated = 4.5%: 11%) were removed from study protocol because of complaints of

gastrointestinal disturbances, depression, fatigue, impotence, and gout. The investigators also examined biochemical side-effects and found a significantly increased incidence of hypokalemia and hyperuricemia in the treated population. The dropout rate was similar in the two groups and averaged 15% during the period of follow-up.

The authors concluded that treatment is definitely indicated in all patients with a diastolic blood pressure greater than 104 mmHg and in patients with a diastolic blood pressure of 90-104 mmHg who are at increased risk because of age or evidence of cardiovascular disease. They added that the possibility of side effects -- symptomatic or biochemical -- must be weighed against the benefit to be expected from treating hypertensive patients who are at low risk (diastolic blood pressure of 90-104 mmHg and without other risk factors).

Commentary

The investigators did find a statistically significant difference in cardiovascular-related morbidity between treated and untreated patients in this, the first, study of mild hypertension (diastolic blood pressure = 90-114 mmHg); however, there are many methodologic deficiencies in this study. The target population was poorly identified -- rather than screening the general population, the investigators chose to recruit the study population from people who had maintained elevations in blood pressure (diastolic blood pressure of 90-114 mmHg) while hospitalized. Smith (58)

has argued that this range of diastolic blood pressure in a hospitalized patient corresponds more closely to a pressure of 100-120 mmHg when measured in an outpatient setting. While it is important not to exclude patients with prior cardiovascular disease, this study had an especially large proportion of such patients (58%) chiefly because subjects were selected from a hospitalized pool of patients rather than the general population. Unfortunately, through demographic data was presented, data for co-morbid risk factors such as hyperlipidemia, smoking, and diabetes mellitus was not provided. The selected population was further limited in that uncooperative or unreliable patients were eliminated during a pre-randomization observation period. Lastly, women were not considered in this study.

Treatment was randomly assigned and administered in a double-blind manner in this placebo-controlled study. Both the placebo and the experimental regimen were clearly defined and compliance with the assigned regimen was monitored. Although the design of the trial was such that alerations could be made in the therapeutic regimen, the initial administration of a triple-agent regimen to all subjects in the experimental group far from approximate contemporary clinical practice. This protocol may have been partially responsible for the high incidence of hypotensive side effects seen in the actively treated group. Ancillary therapy was neither prescribed nor monitored. Despite limiting mild

hypertension to patients with a diastolic blood pressure of 90-114 mmHg, patients in the control group were allowed to maintain a diastolic blood pressure of up to 124 mmHg before active therapy was instituted, i.e. patients in the control group were allowed to progress to a more severe form of hypertension with its associated greater risk but continued to be compared with patients in the actively treated group whose blood pressure had been maintained at or below entry levels. The authors noted that pharmacologic intervention had prevented the elevation in blood pressure beyond 124 mmHg seen in approximately 10% of the control group, however, close supervision could have achieved the same end.

The investigators developed an inclusive list of well-defined trial end points. However, their attempt to separate outcome events into those attributable to hypertension and those attributable to atherosclerosis was somewhat artificial. One of the chief strengths of this study was that attack rates and therapeutic effectiveness were analyzed according to multiple prognostic factors: age, degree of diastolic blood pressure elevation, and evidence of cardiovascular abnormalities. While it is of interest to assess the influence of these factors either individually or in combination, it must be noted that stratification of the patient population into small subgroups increases the likelihood of large errors in observed rates due to random fluctuation, especially when the trial population is small as it was in this study. Prognostic stratification can provide useful

information, however, particularly in a heterogeneous population where the patients are at highly variable degrees of risk. Indeed stratification of this trial population by entry blood pressure suggested that there was no statistically significant difference in cardiovascular-related morbidity between treated and untreated patients with a diastolic blood pressure less than 104 mmHg.

While the authors provided data for the incidence of acute side-effects of treatment, the long-term follow-up was inadequate. Over 11% of the patients in the actively treated group were withdrawn from treatment due to serious side-effects. Unfortunately, this trial did not consider subjective changes in functional capacity or the quality of life, subtle changes which may have contributed to the nearly 15% drop-out rate.

UNITED STATES PUBLIC HEALTH TRIAL (36)

Summary

In this study, the eligible population was selected from among 1600 screened patients "said to have an elevated blood pressure" (36). The screening process yielded 389 subjects (24%) between the ages of 21-55 with a diastolic pressure of 90-114 mmHg (while not receiving anti-hypertensive therapy). Admission criteria included: no evidence of end-organ disease (e.g., renal insufficiency, retinopathy, left ventricular hypertrophy) by history, physical exam, or paraclinical studies; and no evidence of co-morbid risk factors such as diabetes mellitus and hyperlipidemia. Forty-one percent of the

subjects had a history of treated hypertension. The admitted trial study group (see Table 2) was randomly assigned to receive either active treatment (193), consisting of chlorthiazide and rauwolfia serpentina, or placebo (196) and was then followed systematically for an average period of 7 years (see Table 3). Treated patients achieved a mean reduction in diastolic blood pressure of 10 mmHg which was maintained throughout the trial; in contrast, there was no mean change in the diastolic blood pressure in those patients receiving the placebo (see Table 4). There were 4 deaths during the trial (2 in each regimen) and 13 major morbid events with 6 in the treated group and 7 in the control population. The incidence of minor events (retinopathy, cardiomegaly, left ventricular hypertrophy, transient ischemic attacks, evidence of renal failure) was not evenly distributed however (active: placebo = 9.8%: 20.8%). When a patients blood pressure increased to levels of 130 mmHg or greater, he/she was classified as a "treatment failure" and started on active therapy; 12 such cases occurred in the placebo group as compared to none in the actively treated group. Though not well characterized 23(5.9%) participants were withdrawn from the study because of "drug intolerance" -- 19 in the actively treated group and 4 in the placebo group. The overall drop-out rate was 33.9% but there was very little difference between the compared treatments.

The authors of the study concluded that careful follow-up with dietary management and control of other risk factors (e.g., smoking) was a viable alternative to pharmacologic intervention,

given the small degree of risk associated with this disorder and the failure of pharmacologic therapy to protect against atherosclerotic disease.

Commentary

In this trial, there was no difference between treated and untreated subjects in the incidence of deaths or cardiovascular-related morbidity. There was a greater frequency of minor events in the untreated group, but the difference was not statistically significant and the detection of these "softer" end points is more readily biased. The validity of the findings of this trial are enhanced by the fact that allocation of patients was random and that treatment was administered in a double-blind fashion. The compared regimens were well-described and compliance with the assigned regimen was regularly followed. A disadvantage of this study is that the experimental protocol was relatively inflexible with no provisions mentioned for altering dosage or choice of medication; this may have contributed to the high incidence of drug-related side-effects.

Patients in the placebo group were allowed to continue without active treatment until their diastolic blood pressure exceeded 130 mmHg (on three consecutive visits), despite evidence from earlier studies which had shown that patients with a diastolic pressure of 115-130 mmHg clearly benefit from treatment (12-14). Thus, the design of this study clearly violated the principles of sound clinical practice. Nevertheless, allowing patients in the

placebo group to continue untreated with a diastolic pressure of up to 130 mmHg should have enhanced the likelihood of detecting a difference between the two groups, yet no difference was found.

The selection of outcome events was reasonably thorough and all events were reviewed by a blinded committee. However, the study gave inadequate attention to the issue of side-effects mentioning only that 5.9% of patients were withdrawn from their assigned regimen due to "drug intolerance". There was no reported attempt to look for changes in functional capacity or quality of life. Though there was only a minimal difference in the incidence of withdrawals/drop-outs between the compared treatments, undetected adverse effects of treatment may have contributed to the particularly high drop-out rate.

VETERANS ADMINISTRATION -- NATIONAL HEART, LUNG, AND BLOOD INSTITUTE TRIAL (37)

Summary

This two year feasibility trial was performed to determine whether a large population of mildly hypertensive asymptomatic patients could be identified, enlisted, and maintained on protocol for an adequate period of follow-up. The protocol employed in the feasibility trial was essentially the same as that which was to be used in the full-scale study. To be eligible for admission, subjects had to meet the following criteria: a consistent elevation of diastolic blood pressure (85-105 mmHg), an absence of

demonstrable cardiovascular disease, and a willingness to comply with study protocol. Subjects were required to be between 21-50 years of age. Over 118,000 people were screened for mild hypertension at various locations in the community (e.g., factories, shopping centers); 1012 subjects (.86%) were eventually enrolled in the study. The most common reason for ineligibility was "normotension" (diastolic pressure less than 85 mmHg) -- 88% of all people screened. Accepted patients were randomly assigned to treatment in this placebo-controlled trial and followed for two years. Their pre-treatment characteristics are provided in Table 2. Therapy was administered in a double-blind fashion according to a three step regimen as presented in Table 3. Ancillary measures were not discussed. The difference in diastolic blood pressure maintained between those patients in the experimental group and those in the compared group was similar to the difference achieved in other studies. At four months the difference in mean diastolic blood pressure was 3 mmHg, but by eight months the difference was 8 mmHg.

Only 2 deaths (.4%) occurred during the study; both were in the treated group. There were an additional 5 major morbid events (treated: placebo = .4%: .6%). Although the complete data were not provided, the authors noted that preliminary analysis suggested that minor morbid events were more common in the treated population of patients. "Significant hypertension" was considered

to have developed whenever the diastolic blood pressure exceeded 110 mmHg on four successive visits or 120 mmHg on two successive visits. This occurred in seven subjects all of whom were in the control group and active treatment was instituted for these patients. A total of 1303 side-effects were recorded for the actively treated group in contrast to 693 in the placebo group. There was a significantly increased (> 3 times) incidence of impotence, insomnia, asthenia, and nasal stuffiness in the experimental group suggesting that these side-effects were drug-related. Addtionally, there were significantly more asymptomatic biochemical abnormalities (e.g., hypokalemia, hyperuricemia) in the actively treated group (treated: placebo = 176: 8). The investigators recognized that pharmacologic anti-hypertensive therapy may exert a considerable influence on the quality of life. Despite efforts to quantify or "harden" this data, they were unable to make an adequate measurement. The drop-out rate in this two-year study was 14%.

The authors conclusions consisted of recommendations for the full-scale study. Because they found no difference in mortality or morbidity between the compared groups after two years of follow-up, they suggested that the full-scale trial: 1) have a longer period of follow-up -- 5-10 years; 2) accept patients with a higher range of diastolic blood pressure -- 85-115 mmHg; 3) accept patients with cardiovascular abnormalities. The last two recommendations were

made with the idea of increasing the overall incidence of outcome events and, additionally, to make the study population more representative of the general population of mild hypertensives. The investigators further suggested that all future studies make a more serious attempt to consider the adverse consequences of treatment including subtle changes in the quality of life and the incidence of long-term side-effects.

Commentary

In this study with a follow-up period of two years, there was no difference in mortality or morbidity between treated and untreated patients. The excellent design of this trial helps to ensure the scientific validity of the results. The target population was identified, and all population transfers were well-defined. Treatment in this placebo-controlled trial was assigned randomly and administered in a double-blind fashion. The compared populations had similar pre-treatment characteristics, thus confirming that the allocation process was effective. Both the experimental regimen and the placebo were well-described and provisions were made to adjust the therapeutic regimen as pressure-considerations or side-effects warranted. Patients with increasing blood pressures were handled appropriately in this study. When subjects sustainted an elevated blood pressure higher than the stated upper limit accepted for mild hypertension, active treatment with known pharmacologic agents was instituted.

A wide-range of outcome events was considered: death, cardiovascular-related morbidity, and adverse effects of treatment. Death and major morbid events were compared and found to be similar in the treated and untreated groups, but minor events were incompletely characterized. It was suggested however, that minor events may have been more common in the treated group. One of the strengths of this RCT is its rigorous approach to evaluating the potential adverse consequences of anti-hypertensive treatment. The investigators considered both biochemical and symptomatic side-effects. Of all outcome events considered, it was only for the adverse reactions to treatment that the authors found a statistically significant difference between the compared groups (with more adverse effects among treated patients). In addition, this was the only study which attempted to quantify "soft" data such as subjective changes in quality of life or functional capacity. Unfortunately, the investigators encountered many difficulties and were unable to satisfactorily gather this information.

CHELMSFORD GROUP (38)

Summary

All patients screened in the Chelmsford Group Trial were referred to the clinic by their general practitioners. To be eligible for admission, it was required that subjects: be less than 50 years of age, maintain a diastolic blood pressure of 90-110 mmHg, and be free of symptoms or complications attributable to

hypertension. Two hundred and thirty-three patients satisfied these criteria and were admitted to the trial. Their entry characteristics are provided in Table 2. Patients were assigned in alternate blocks of five to either the active (111) or the control group (122). Patients in the active group received anti-hypertensive medications in a "stepped fashion". By comparison, those in the control group received no treatment whatsoever but were followed at equally frequent intervals (see Tables 3-4). Any subject in the control group who developed and maintained levels of diastolic pressure of 110 mmHg or more was started on active therapy. There were 16 such patients (35%).

Duration of follow-up ranged from 1 to 11 years with an average period of observation of 5.5 years. The mean difference in diastolic blood pressure maintained between the compared groups was not made clear.

There were no deaths in either group during the trial. However, there were a total of 22 major morbid events with 6(5.4%) in the treated group and 16(13.2%) in the control group -- the difference is not statistically significant. Unfortunately, minor events as well as adverse effects of treatment were not considered. The drop-out rate was slightly more than 7%.

The authors concluded that patients with asymptomatic mild hypertension require close supervision particularly if anti-hypertensive medications are not prescribed.

Commentary

This study had negative findings with no statistically significant difference in outcome between treated and untreated patients with asymptomatic mild hypertension. Furthermore, the non-significant trend in major morbid events (treated: untreated = 5.4%: 13.2%) which prompted the investigators to suggest that treatment might be of some benefit in these patients could be attributable to the design of this study. This trial has serious deficiencies in each of the major areas comprising the RCT which compromise its scientific validity.

The population targeted for study in this trial was poorly identified. Evidently, physicians referred patients with suspected hypertension to a screening clinic where serial blood pressures were recorded. (The number of referrals was not stated.) Patients with a diastolic blood pressure in the defined mild range were eligible for admission. The selection criteria were designed to ensure that only subjects with minimal pre-treatment risk were included, so that patients over 50 years of age or those with evidence of end-organ disease were excluded; however, it is unclear whether patients with other risk factors for cardiovascular disease (e.g., smoking, hyperlipidemia, diabetes mellitus) were included because the trial population was inadequately described. The most serious shortcomings, those most responsible for allowing bias to enter the trial, were in the execution of the therapeutic maneuver. Treatment was assigned

by systematic allocation rather than by a strictly random process. Also, the administration of treatment was not blinded as patients in the control group were untreated. There was no mention of ancillary treatment measures for either group. The results of treatment in terms of blood pressure control were not clear; the difference in the mean diastolic pressure achieved between the two groups was not stated. The study was limited to the analysis of "serious events", i.e. congestive heart failure, myocardial infarction, and stroke. Minor end-points and adverse effects of treatment were altogether ignored.

The small difference in trial end-points during this trial between the treated and untreated groups does not support the authors' suggestion that patients with asymptomatic mild hypertension might benefit from treatment, particularly since the design of the trial provided ample opportunity for bias to influence the results in favor of the treated group.

HYPERTENSION DETECTION AND FOLLOW-UP PROGRAM (HDFP) (39-40)

Summary

In the HDFP trial, outcome for subjects receiving systematic anti-hypertensive treatment in program centers ("Stepped Care") was compared to that for persons referred to existing community medical care ("Referred Care"). The trial was designed to detect a 40% reduction in mortality in the "stepped care" group after 5 years of follow-up.

An effort was made to identify hypertensives in the general population. A population-based screening of nearly 160,000 adults from 14 communities in the United States yielded 10,400 subjects (6.8%) for study. To be eligible for admission, participants, 30-69 years of age, had to have a mean diastolic blood pressure greater than 90 mmHg -- patients already being treated for hypertension or those with evidence of end-organ disease were not excluded. (Those selected for study are described in Table 2.) In addition to demographic data, information was provided in regard to the incidence of patients with a history of treated hypertension (25%), evidence of end-orgam disease (5-7%), or co-morbid risk factors (e.g., diabetes mellitus, hypercholesterolemia, smoking). The subjects were randomized to "Stepped Care" (3903) or "Referred Care" (3922) with stratification by entry blood pressure: Stratum I = 90-104 mmHg; Stratum II = 105-115 mmHg; Stratum III = 115+ mmHg. Over 70% of the patients admitted for study were in Stratum I. Since the purpose of this methodologic review is to analyze studies of mild hypertension, further discussion will be limited to the population of patients in Stratum I who were well-matched at entry.

Patients assigned to the "Stepped Care" regimen received a free, standardized program of anti-hypertensive therapy at special clinics established by the HDFP. In an attempt to achieve uninterrupted therapy, regular clinic attendance and compliance with treatment were monitored. The protocol (see Table 3) allowed for changes in the drug dosage or regimen to minimize the adverse effects

of treatment while maintaining control of blood pressure. In addition to pharmacologic therapy, counseling was offered regularly in regard to the importance of diet, exercise, weight reduction, and smoking. The HDFP investigators felt that the results of the VA trials on moderate and mild hypertension made it "inappropriate" to use placebos in large numbers of hypertensives across the full range of severity to be encountered in this community based trial. Thus, it was decided not to deny pharmacologic therapy to any patient. Subjects randomized to the "Referred Case" group were referred for treatment to their usual sources for medical care. (Special efforts were made to ensure that patients with severe hypertension would receive treatment.) Whereas patients in the "Stepped Care" group were seen in HDFP clinics at least every four months, patients in the "Referred Care" group were seen only once a year.

Due to the design of this trial, patients in both groups were eligible to receive anti-hypertensive treatment, and the mean difference in diastolic pressure maintained between the compared groups during the 5 years of the trial was only 5 mmHg. However, there was consistently a greater proportion of patients receiving pharmacologic treatment in the "Stepped Care" group ("Stepped Care: Referred Care" = 66-75%: 40-54%), and more subjects in the "Stepped Care" group maintained a diastolic pressure in the "normotensive range" -- less than 90 mmHg. ("Stepped Care: Referred Care" = 60%: 40%). It was not stated whether the failure of patients in the "Referred Care" group to receive treatment was unintentional

(e.g., inadequate follow-up, poor compliance) or a result of deliberate medical policy. Patients were permitted to continue in the "Referred Care" group without treatment until their diastolic pressure exceeded 115 mmHg (not 104 mmHg). At this point, special efforts were made to ensure that these patients would receive treatment. However, "Referred Care" patients were seen in HDFP clinics only once a year so that the ability to detect patients with elevated pressures was somewhat limited.

Death was selected as the primary end-point in the HDFP trial. The investigators found a statistically significant difference ($P < .01$) between the compared groups in the number of deaths during the 5 year follow-up period (SC: RC = 5.9%: 7.4%). There were 26% fewer cardiovascular deaths in "Stepped Care" than in "Referred Care" subjects and 13% fewer non-cardiovascular deaths. The authors failed to find a significant reduction in mortality in each subgroup when subjects were stratified by race and/or sex. For example, in white women there was less than a 5% reduction in all-cause mortality for those subjects in the "Stepped Care" group. In addition, for men and women less than 50 years of age, no benefit was seen.

In an effort to obtain objective evidence of non-fatal secondary end points, the investigators collected data reflecting target organ damage (e.g., electrocardiogram, serum creatinine levels, chest radiographs) however, this information has not been reported.

The authors suggested that the experience of the Hypetension Detection and Follow-up Program demonstrated an ability to identify a high percentage of hypertensive persons in the general population and maintain most of those detected in a long-term control program. The results of the trial led the investigators to conclude that the systematic effective management of hypertension has a great potential for reducing mortality for the large number of people with elevated blood pressure in the general population, including those with mild hypertension.

Commentary

This trial was designed for the purposes of determining whether: 1) a substantial proportion of all hypertensives in the general population could be identified; 2) those patients found to be hypertensive could be maintained on long-term anti-hypertensive therapy aimed at reducing blood pressure to nomotensive levels; 3) a systematic approach to anti-hypertensive therapy (Stepped Care) would be more effective in reducing risk of five year mortality for all hypertensive adults compared to routine medical care available in the community (Referred Care). The purpose of this trial was not to prove that patients with hypertension (including mildly hypertensive patients) benefit from anti-hypertensive therapy. The investigators had been persuaded by the evidence in earlier studies that patients with any degree of diastolic pressure elevation are at increased risk and benefit from treatment; therefore,

they felt that it would be unethical to deny pharmacologic therapy to such patients. Consequently, they developed a scheme whereby therapy would be potentially available to all subjects -- participants were randomized to either "Stepped Care" or "Referred Care" The investigators estimated, however, that fewer patients in the "RC" group would receive treatment because of uncertainty in the general medical community on the value of treating mild hypertension and a less systematic approach to treatment (e.g., less frequent follow-up, poorer compliance). Indeed, fewer patients in the "RC" group did recieve treatment. However, because patients in this group were treated outside the study, the type of care they received, particularly with regard to ancillary therapy, remains somewhat of an unknown and subject to a high degree of variability. Several other design consequences followed from the decision not to have a placebo control group:

1) It was going to be more difficult to detect a significant difference in outcome atrributable to this risk factor given that the difference in the mean diastolic pressure would be attenuated by treatment of a large proportion of members in the "RC" group. Systematic ancillary therapy of co-risk factors for subjects in the "SC" group should have further limited the authors willingness to ascribe differences in outcome to the small differences in mean diastolic pressure maintained between the two groups during this trial.

2) Death from all causes was designated as the sole endpoint of this trial. As "SC" subjects were seen more frequently, it was decided that it would be improper to compare the incidence of morbid events (e.g., episodes of congestive heart failure, stroke, myocardial infarction) because prevention, and more importantly detection, of these outcome events might be related to how frequently subjects were observed. As a consequence, an important consideration -- morbidity -- was omitted.

3) The incidence of adverse effects of treatment could not be compared. In a study involving large numbers of often young people being exposed to pharmacologic events for long periods of time, it is unacceptable not to consider side-effects. The adverse consequences of treatment must be considered as well as the potential benefits.

Nonetheless, the authors found a statistically significant difference in mortality between the two groups. They emphasized that the proportional risk reduction for members of the "SC" group was 20%, however, the absolute difference in mortality was small -- 1.5%. The benefits of the "SC" regimen were not limited to the prevention of cardiovascular deaths (proportional risk reduction = 26%) as there was a 13% reduction in non-cardiovascular deaths. This finding would seem to indicate that the differences in mortality rate observed between the two groups was due to factors other than anti-hypertensive therapy. Possible explanations for

better outcome in the "Stepped Care" group might include: 1) the SC group was a healthier population at baseline (e.g., due to ineffective randomization); 2) the SC group received superior general medical care. In addition, the benefits of "Stepped Care" were not evenly distributed; white women and all subjects under 50 years of age failed to experience reduced mortality despite the lower pressures achieved through "Stepped Care". Over 25% of the patients admitted to this study were already on antihypertensive therapy and thus, if left untreated, would have had more severe hypertenstion than their entry pressure suggested. Additionally, approximately 5% of the trial population had evidence of cardiovascular disease at the time of entry. It would be important to further analyze the data to see if benefit from treatment was restricted to these patients at increased risk.* It would also be helpful to examine the data dividing the patients into subgroups on the basis of entry diastolic pressure: 90-94 mmHg, 95-99 mmHg, and 100-104 mmHg.

*In a presentation to the American College of Cardiology in March of 1980, one of the investigators, Jeremiah Stamler, M.D., presented the findings of subsequent analyses indicating that mortality was over three times higher in those with target-organ damage at entry than in those without it; in addition it was higher in the 25% of patients who entered the trial already on antihypertensive therapy. Unfortunately, this information is not available for closer scrutiny as it has not been published.

OSLO STUDY

Summary

In identifying the potential study population, the investigators attempted to screen all men living in Oslo between the ages of 40 to 49 years (≈2500). A response rate of 65% produced 16,200 men for screening of whom 785 (5%) were eventually randomized. Unlike most of the trials, this study incorporated both the systolic and diastolic blood pressure in defining mild hypertenstion: a systolic pressure of 150-179 mmHg or a diastolic pressure of 95-110 mmHg. As a result, over 12% of the study population had a diastolic blood pressure less than 90 mmHg. Two hundred and fifty-seven men who would have been eligible for admission to the study on the basis of their blood pressure were excluded by a rather extensive list of rejection criteria: a history of previously treated hypertension, evidence of cardiovascular disease, coincident malignant or chronic illness, evidence of target organ damage (e.g., electrocardiographic findings consistent with cardiac abnormalities), ethanol abuse, or social maladjustment.

Accepted patients were randomized to receive active treatment (406) or no treatment at all (379). The experimental regimen began with a diuretic to which either methyldopa or propranolol could be added in variable dosage (see Table 3). A statistically significant difference between the two groups of

10 mmHg in mean diastolic pressure was maintained throughout the 5 year period of observation (see Table 4). Over the course of the study there were 19 deaths which were evenly distributed between the two groups (see Table 5). The total number of major morbid events was 20(2.6%) with 8 events (20.0%) occurring in the treated group as compared with 12(3.2%) in the untreated group. There was a similar incidence of minor morbid events (treated: untreated = 1.6%: 3.2%). There was no significant difference in mortality or in the overall incidence of cardiovascular events between treated and untreated participants. However, when the investigators stratified the study population on the basis of pre-treatment blood pressure into "high-risk" (diastolic pressure > 100 mmHg) and "low-risk" groups (diastolic pressure < 11 mmHg), they found there was a non-significant decreased incidence of cardiovascular events among "high-risk" patients ($P = .06$) but not "low-risk" patients ($P > .10$).

Patients in the control group were not allowed to continue untreated when their blood pressure exceeded the study limits established for mild hypertension. During the 5 year trial period, 65 untreated men (17%) required pharmacologic intervention. Investigators tried to minimize the occurrence of side-effects by employing a protocol with inherent flexibility, and they reported finding "no serious drug-induced" disease. However, there was a significantly greater proportion of patients

in the treated population with complaints of drowsiness, fatigue, impotence, and/or gout. Indeed, methyldopa caused drowsiness and fatigue in 41% of the patients and so was substituted for by propranolol. The overall drop-out rate was only 1.7%.

The authors of this study concluded: 1) that anti-hypertensive treatment confers significant protection against "pressure-related" events (e.g., stroke, congestive heart failure, left ventricular hypertrophy); 2) there was no protection against atherosclerotic coronary artery disease; 3) there was no effect on overall cardiovascular morbidity; and 4) patients at "high-risk" (diastolic blood pressure > 100 mmHg) at the time of entry probably benefited from therapy.

Commentary

This is yet another trial with essentially negative findings as there was no difference between treated and untreated patients in the incidence of deaths or overall cardiovascular morbidity. The authors' did show a statistically significant difference between the compared groups in the incidence of "pressure-related" cardiovascular events. However, this distinction is artificial and really does not provide added information. Regardless of the findings for "pressure-related" events, if there is no benefit from treatment against overall cardiovascular morbidity, then treatment is not indicated. The investigators' nearly significant finding (P = .06) is potentially

of great importance, but the design of the trial allowed for ample opportunity for bias to influence the results. The major defect in the design of the stratified analysis is the non-blinded assessment of outcome events as both the physicians and the patient were aware of the assigned treatment. This disregard for double-blind administration of treatment renders the assessment of non-fatal outcome events particularly susceptible to bias.

The design of this trial allows for unequal detection of not only non-fatal trial end points but also adverse effects of treatment. The adverse effects of treatment were poorly characterized, and their incidence was not discussed other than mention of an "increase" in complaints of fatigue, impotence, and gout in the treated group. Subjective changes in functional capacity or quality of life were not monitored in this study.

AUSTRALIAN STUDY (41)

Summary

The Australian National Blood Pressure Study was designed to detect a 30% reduction in morbidity and mortality over 5 years of follow-up in treated patients with asymptomatic mild hypertension. In order to generate a trial population, screening centers were established at several locations throughout the community including public buildings and places of business. Volunteers from the general population between 30-69 years of

age had their blood pressure measured. Subjects were eligible for admission if their diastolic blood pressure fell between 95-110 mmHg providing that they had not already been receiving anti-hypertensive medications. However, an effort was made to exclude all people with evidence of end-organ disease (e.g., myocardial infarction, angina, stroke, renal failure). Additional exclusion factors included: co-existing terminal illness; a primary cause of hypertension; or the presence of diabetes mellitus, gout or asthma. Of 104,171 volunteers screened, 3931 were randomized, but 504 subjects were later eliminated from the study because their post-randomization diastolic blood pressure fell below the study threshold of 95 mmHg making them ineligible to begin treatment under the study protocol. The size of the final trial population was therefore 3427 or 3.3% of those screened. The characteristics of the trial population are provided in Table 2. Patients were randomly allocated, with stratification by age and sex, to either the active regimen (1721) or the placebo (1706) but treatment was administered in a single-blind fashion with patients unaware of the treatment they were receiving. The compared groups were well-matched at entry. The protocol called for a "stepped care" approach so that anti-hypertensive medications could be adjusted until blood pressure was brought under control. If participants in either group developed and maintained a diastolic blood pressure above the threshold of 110 mmHg, these subjects were classified

under "pressure limits exceeded", and definitive anti-hypertensive treatment was given. This was not considered an outcome event and these subjects, 198 in the placebo group and 4 in the actively treated group were kept in the study. All subjects were given advice on weight, diet, and smoking irrespective of the regimen to which they had been randomized. The mean duration of follow-up was 4 years. During this time, the mean difference in diastolic pressure between the treated and untreated groups was 6 mmHg (see Table 4).

A wide range of cardiovascular-related outcome events was considered and all such events were reviewed by a blinded committee. The analysis of trial end-points was done in two ways. In the "on treatment" approach, account was taken only of those trial end-points occuring while subjects were continuing their regimen. In the "intention to treat" approach, account was taken of all trial end-points regardless of whether or not participants had remained on their assigned regimens. In presenting the results of this RCT, I will focus on the data provided by the latter approach for three reasons: 1) the advantages of the initial randomization are preserved; 2) the "on treatment" analysis ignores a large segment of the study population as over one third of the participants prematurely discontinued their assigned regimen; 3) Reader et al. (54) have pointed out that the "on treatment" analysis was: "based on 'softer' data as a

higher proportion of fatal than non-fatal events occured after withdrawal".

During the course of this trial, there were 26 deaths (.8%) with 8 occurring in the experimental group and 18 in the compared group. The number of major morbid events was evenly distributed between the two groups with an overall incidence of 2.4%. Minor events were nearly twice as common (4.8%) and were more frequent in the control group (see Tables 5-7). The difference between the compared groups only achieved statistical significance ($P < .05$) when all events were considered together. Over two thirds of all trial end-points were due to ischemic heart disease, predominantly non-fatal events, which occurred in similar numbers in the active and placebo groups. Only preliminary information was provided on the differences in attack rates for prognostic subgroups. These comparisons were performed using data from the "on treatment" analysis, and the numbers of trial end-points were small in some subsets. Treatment appeared to be of most benefit in men and in all subjects over the age of 50. Trial end-point rates increased with the average diastolic pressure recorded throughout the trial in both treated and untreated patients.

The authors concluded that treatment is efficacious in reducing morbidity and mortality secondary to cardiovascular disease in patients with asymptomatic mild hypertension. However,

they found that the majority of outcome events was related to ischemic heart disease where treatment seemed to be of little benefit; the investigators suggested that trials with longer periods of follow-up might be necessary: 1) a longer period of follow-up, with treatment beginning at an earlier age, might have a greater chance to influence the natural course of ischemic heart disease; 2) an extended period of follow-up would allow the occurrence of a sufficient number of events to demonstrate therapeutic benefit. They noted that this might pose ethical problems, however, given that they considered there to be overall benefits of treatment.

Commentary

This ambitious study screened over 100,000 people but less than 4% were found to be eligible for admission. The target population was well-identified -- those screened were members of the general population between 30-69 years of age. After multiple visits, subjects found to have a mean diastolic pressure of 95-110 mmHg were asked to join the study. Variability within the trial population was limited by admission and rejection criteria designed with the clear intent of excluding patients with co-morbid conditions (e.g., diabetes mellitus) or evidence of cardiovascular disease. Undoubtedly, these criteria were in large part responsible for the small percentage of patients admitted to the study.

Information detailing the compared regimens was furnished, and treatment was applied in a clinically appropriate manner: 1) a "stepped care" approach was employed: 2) irrespective of the assigned regimen, patients were followed until their blood pressure exceeded the defined mild range at which point definitive treatment was given; 3) all subjects were given advice on weight reduction, diet, and smoking. There was random allocation of treatment with stratification by age and sex though not by entry blood pressure. This process appeared to be reasonably effective as the compared groups were well-matched at entry. The fact that over one-third of the trial population prematurely discontinued their assigned regimen may have disturbed the even distribution of patients achieved by the initial randomization process. More importantly, however, this striking inability to maintain patients on study protocol brings to light two other serious deficiencies in this trial:

1) In the actively treated group, the premature interruption of study protocol was most often patient-initiated, yet reasons for the discontinuation of active treatment were not addressed. In this trial, the adverse effects of treatment were altogether ignored; not even were the more readily predictable short-term side-effects of treatment considered. Adverse effects of treatment may have contributed to the withdrawal of some of these patients.

2) Though not a majority, a large percentage of patients who withdrew from the placebo group did so at the suggestion of their physician. In a single-blind study, the physician's objectivity is compromised and this can introduce bias into the study both in the performance of the maneuver and in the detection of outcome vents, particularly the more subjective ones.

The large number of subjects violating study protocol also created problems in interpreting the results, prompting the investigators to analyze the data in two ways, the "intention-to-treat" approach and the "on treatment" approach. However, there are problems with both analyses. (The deficiencies of the "on treatment" approach have been previously mentioned.) Though the "intention-to-treat" approach preserves the benefits of the randomization process, both groups are significantly contaminated by patients who have switched treatment.

The authors did not achieve their goal of demonstrating a 30% reduction in morbidity and mortality in treated patients with asymptomatic mild hypertension in either of the two analyses. Indeed, the data they provide does not justify their conclusion that treatment is efficacious in reducing morbidity and mortality in patients with this disorder. The difference in deaths was not significant, and major cardiovascular end-points were evenly distributed between treated and untreated patients. The biggest difference between the compared groups was in the

incidence of minor morbid events, and it was only when these outcome events were considered in the analysis that the overall results achieved statistical significance. Morbid events, particularly the minor ones, may have been detected unequally however because of single-blind observation.

JAPANESE STUDY (43)

Summary

This prospective study was performed to evaluate the efficacy of long-term anti-hypertensive therapy in elderly patients with mild hypertension. The subjects screened were residents of convalescent homes, and all were over the age of 60. Following the discontinuation of any anti-hypertensive medications, serial blood pressure readings were recorded, and those patients with an average diastolic blood pressure of 90-110 mmHg or an average systolic blood pressure of 160-200 mmHg were accepted into the trial. Because both the systolic and diastolic pressure were incorporated in their definition for mild hypertension, only 56% of the study population had a diastolic blood pressure greater than 90 mmHg. The mean diastolic pressure for all participants was 86 mmHg. Apparently, age and blood pressure were the only requirements for admission. Ninety-one patients were selected for study -- their entry characteristics are provided in Table 2. Participants were started on either active treatment (44) or a placebo (47); the regimen was assigned on the basis of matched

pairings which took into account age, sex, and entry blood pressure. Whether treatment was blinded is unclear, however, treatment was administered in accordance with a "stepped" approach. During the four-year follow-up period, a difference in diastolic blood pressure of 7 mmHg was maintained between the compared groups (see Table 4).

Over the course of this study, there were 14 deaths (18%) -- 7 in each group. There was one major event (2.3%) in the treated group as opposed to 6(12.8%) in the untreated group. Data for minor events was not presented (see Table 5-7). Subjects were removed from the trial when their blood pressure became elevated above 200/110 mmHg. There were 8 such cases -- all were in the placebo group (19%). Only when these cases were treated as trial end-points did the authors find a statistically significant difference in cardiovascular complications between the compared groups. The investigators recorded other non-cardiovascular complications during the follow-up period (e.g., malignancies, infections, bone and joint diseases). There were 12(32%) such events in the experimental group and 17(42%) in the placebo group. These complications were 2 to 3 times more prevalent than the cardiovascular-related complications. Side-effects other than asymptomatic biochemical fluctuations (e.g., hypokalemia, hyperuricemia) were not monitored in this study. The overall drop-out rate was 13% as 6 subjects were lost from both groups.

The authors suggested that anti-hypertensive treatment is effective in elderly patients with mild hypertension but that careful follow-up is necessary not only for cardiovascular complications but for general health considerations as well. A statistically significant difference in the number of cardiovascular complications was found between the treated and untreated groups when the elevation of blood pressure beyond study limits was treated as a trial end-point.

Commentary

The Japanese trial had substantial problems in design and analysis. Few of the experimental principles which have been developed to minimize the occurrence of bias in randomized clinical trials were adhered to in this prospective study. The target population was inadequately described, and the number of people screened was not stated. The authors failed to delineate the admission/rejection criteria used to select the population for study. More importantly, those patients who were admitted were insufficiently characterized; key elements such as the incidence of demonstrable target organ disease or co-morbid risk factors (e.g., diabetes mellitus, hyperlipidemia, smoking) were not proved. In addition, some of the patients had a known history of hypertension for which they had been receiving treatment, but the overall prevalence or mean duration were not mentioned. Collectively, this lack of information makes it

difficult to determine how representative the study population is of elderly mildly hypertensive patients, and whether the allocation process created groups with equal prognostic risk.

Treatment was assigned on the basis of matched pairings of patients. Unlike a truly random process, this method cannot ensure that bias will not take place during the allocation of treatment. Though the study was placebo-controlled, no mention was made of whether therapy was administered in a double-blind fashion. Thus, the detection of outcome events, particularly non-fatal ones, may have been somewhat unreliable. The experimental regimen utilized a "stepped" approach in which anti-hypertensive medications were adjusted according to blood pressure. Regardless of the assigned regimen, definitive anti-hypertensive treatment was given when the blood pressure exceeded 200/110 mmHg. There was no discussion of whether compliance was monitored.

The investigators observed both cardiovascular-related events and non-cardiovascular-related events (e.g., infections, psychiatric disorders, cancers, bone and joint diseases). They noted a statistically significant difference in cardiovascular-related end-points between the compared treatment groups. However, this finding is somewhat misleading because in their analysis of trial end points, the authors included eight subjects from the placebo group who had been started on active treatment in response to an elevated blood pressure. When these patients are removed

from consideration, there is little difference between the treated and untreated groups. In addition, there was a relatively even distribution of non-cardiovascular-related events which were two to three times more common than cardiovascular-related end-points. Possible adverse effects of treatment were not considered in this trial.

The results of this trial would seem to suggest that anti-hypertensive treatment is not indicated in elderly patients with mild hypertension, but rather that careful general medical follow-up is needed.

DISCUSSION

There is a consistent set of methodologic problems in the designs of the eight completed randomized clinical trials of mild hypertension. These deficiencies involve issues in both internal validity and external generalizability and are in large part responsible for the failure of these studies to provide definitive answers for determining which mildly hypertensive patients will benefit from therapy. At this point, I would like to briefly review these methodologic problems -- the purpose of this review is not merely to reiterate the methodologic requirements of RCTS as stated in the Methods section of this thesis, but rather to focus attention on common deficiencies which contribute to the current state of confusion regarding issues in the management of mild hypertension.

A. Research Objectives

Comparison of the eight trials of mild hypertension is made difficult by the fact that the research objectives of the individual studies were highly variable. The first study, the VA-Cooperative Group Study, was designed to determine whether anti-hypertensive therapy was effective in reducing cardiovascular-related morbidity in mildly hypertensive patients (diastolic blood pressure = 90-115 mmHg). The findings of this study led to the widely accepted conclusion that a diastolic pressure of 105 mmHg or greater was an indication for life-long pharmacologic intervention. Thereafter, research attention shifted to people who were at lower risk -- those with smaller elevations of diastolic pressure (< 105 mmHg) and free of evidence of end-organ disease (e.g., USPH, Australian, Oslo trials). The Japanese study was further limited in that it was concerned with the efficacy of anti-hypertensive therapy in elderly mildly hypertensive patients (> 60 years of age).

The VA-NHLBI trial was not designed to determine whether pharmacologic anti-hypertensive therapy reduced morbidity and mortality in mildly hypertensive patients. Rather, the major purpose of this two-year feasibility trial was to determine whether a large population of asymptomatic mildly hypertensive patients could be identified, enlisted, and maintained on study protocol for an adequate period of follow-up; unfortunately, the full-scale trial never followed. Similarly, the intent of the HDFP study was not

to determine whether anti-hypertensive treatment was efficacious in mildly hypertensive patients, for the findings of earlier studies had convinced these investigators that treatment was indicated in such patients. Hence, the HDFP trial was designed to determine how mildly hypertensive patients could be best identified and how anti-hypertensive treatment could then be best administered. As a consequence of these different purposes, each of the studies incorporated different features of research design. Nevertheless, all studies recorded and analyzed their data for the effects of treatment on mortality, and all but one study reported data on morbidity. Thus, comparisons of the trials and their treatment effects are possible.

B. Baseline State Considerations

Insufficient measures have been taken to ensure that the effects of treatment were compared in subjects with similar risks for suffering morbid events. One of the key elements of the prospective randomized clinical trial is the random allocation of treatment, yet in 2 of the 8 studies, treatment was not assigned in a strictly random manner. Thus, allocation bias cannot be discounted in these two trials. The efficacy of the allocation process, regardless of its nature, has been difficult to confirm in each of the studies because identification of the study populations has been generally inadequate with insufficient attention given to co-morbid risk factors and gradations in the severity of hypertensive disease.

To ensure further that treatment is compared in patients at equal risk, investigators can subdivide the compared populations into prognostic subgroups. Despite the advantages offered by prognostic stratification, only 4 of the 8 studies elected to analyze their data in this manner. In those studies which did employ this technique, the investigators' abilities to effectively stratify their study populations was limited by not only inadequate identification of the clinical characteristics, but also the relatively small size of the compared populations. Descriptions of populations of mildly hypertensive patients to be studied must be more complete, and new indexes for prognostic strata must be developed so that the results can be compared within homogeneous strata of "high" and "low" risk patients.

C. Performance of the Therapeutic Maneuver

In all the phases of the randomized clinical trial, the investigators have a responsibility to fulfill the often opposing principles of scientific validity and clinical applicability. In performing the therapeutic maneuver, they must ensure that the compared treatments are applied equally and at clinically suitable levels of proficiency. In several studies, these principles were compromised. All of the studies monitored for the primary effect of anti-hypertensive therapy (i.e. changes in arterial blood pressure). However, two (see Table 3) of the

studies employed clinically inappropriate experimental protocols, since all patients were given the same fixed regimen. In addition, ancillary measures (e.g., salt restriction, weight reduction) which can potentially play an important role in blood pressure reduction (59), were largely ignored with five of the trials failing to even mention whether or not ancillary measures were employed.

Another issue has to do with the initiation of treatment for patients whose blood pressure rises above pre-defined study limits. All of the studies defined a threshold of diastolic pressure beyond which any patient would be given definitive anti-hypertensive therapy irrespective of their assigned regimen. However, this threshold corresponded to the upper limit used to define mild hypertension in only half of the trials. In four of the studies, subjects in the control group were allowed to continue in the trial untreated when their blood pressure exceeded the defined mild hypertensive range thereby enhancing their risk for suffering a cardiovascular event. In addition to being clinically inappropriate, the delayed institution of active therapy has the potential for magnifying the observed difference in outcome between treated and untreated patients.

D. Selection, Detection, and Analysis of Outcome Events

The event(s) chosen as the main outcome of a clinical trial must be suitably selected to be clinically meaningful,

but at the same time statistically countable. Following the selection of outcome events, the investigators must then ensure that there is equal detection. The design and the analysis of the studies performed thus far are better suited to decisions in public health (numbers of cardiovascular deaths prevented nationwide) than in personal health. While death is the "hardest" of end points, the risk of death to the individual with mild hypertension is quite small; however, it is more likely that he/she will suffer a non-fatal morbid event. Hence, non-fatal cardiovascular complications should receive major consideration as trial end points for they are more pertinent to issues in personal health. However, steps must be taken to ensure that these "softer" trial end points are rigorously defined so that their detection is reliable and reproducible.

The detection of outcome events should not be limited to only the potential benefits of treatment but rather should include possible adverse consequences of treatment. Yet the mild hypertension trials display a common lack of concern for adverse effects of anti-hypertensive treatment. Only 4 of the 8 studies looked for short-term side-effects of therapy, and each of these four found a significant increase in the treated group. None of the studies attempted to determine whether there were subjective changes in quality of life or functional capacity, nor did any study consider possible side-effects secondary to

long-term exposure to anti-hypertensive medications. In screening for short-term adverse effects of treatment, biochemical as well as symptomatic side-effects should be considered. In addition, dependable indexes need to be developed so that information regarding subtle changes in functional capacity and quality of life secondary to drug therapy can be quantified.

The problem of long-term side-effects had not been recognized until recently. They are often unpredictable occuring only after years of drug exposure. The ongoing MRC trial has issued a report stating that a significant number of treated patients developed peripheral vascular disease after two years of anti-hypertensive therapy for mild hypertension (62). In addition, beta-blocking agents are known to raise serum triglycerides and lower high density lipoproteins (66), effects which have been shown to be associated with an increased risk of ischemic heart disease (67,68). Information on possible adverse effects due to long-term drug exposure is just beginning to appear -- most likely the risk of adverse effects from chronic anti-hypertensive therapy is small but as Oliver has recently reminded us: "... the risks involved in correcting risk must be compared with the risk of the disease itself" (63).

As previously mentioned, following the selection of outcome events, measures must be taken to ensure that outcome is equally detected. After developing precise definitions for

outcome events, the investigators must see that these definitions are applied uniformly to the compared groups. This requires that the physician and the patient are unaware of which treatment the patient received. In 4 of the 8 trials, this methodologic precaution was not taken (see Table 3). Thus, in these trials, non-fatal end-points and the assignment of cause to fatal end-points must be viewed as being unreliable as the observers objectivity cannot be guaranteed.

E. Generalizability

For the results to be clinically meaningful to the practicing physician, the population selected for study must be representative of the general population of mildly hypertensive patients. There is evidence, however, that such was not the case in these completed trials of mild hypertension. According to the United States National Health Survey, approximately 20% of the adult population has a diastolic pressure of 90-109 mmHg, yet none of the four population-based trials (USPH, HDFP, Australian, Oslo) yielded more than 5% of the subjects screened. There are two possible explanations. One is that the 20% population estimate is much too high. However, the more likely explanation is that the yield in these studies was low primarily as a result of restrictive eligibility criteria which limit the available population. The eligibility criteria should not serve to exclude patients from a study on the basis of factors

which contribute to overall risk for suffering trial end points (i.e. cardiovascular disease). This ignores a critical element of this disorder, one which makes its study so difficult -- heterogeneity within the population of mild hypertensives. The problem of heterogeneity can be more effectively addressed by accepting a wider range of patients into the study who can then be stratified into prognostic subgroups as previously discussed. When analyzing the results, outcome can be compared across these prognostic subgroups, thus enhancing our chances of identifying those mildly hypertensive patients who will benefit from anti-hypertensive therapy.

With these methodologic deficiencies in mind, I would now like to quickly review the evidence which has been gathered to date looking first at mortality alone and then at all trial end points.

A. Mortality

Seven of the eight completed trials of mild hypertension failed to find clinically substantial or statistically significant differences in the number of deaths between treated and untreated patients. Only one study, the HDFP trial, found a significant reduction in the number of deaths in a group of patients who had uniformly received anti-hypertensive therapy with rigorous follow-up. Subjects in the compared group were referred to their usual source of medical care, and many of these patients received

anti-hypertensive treatment. As such, this study was not designed to determine whether anti-hypertensive treatment is efficacious in mildly hypertensive patients, but rather to determine how these patients could best be identified and maintained on treatment for an extended period of time. Hence, this study essentially compared two health care delivery systems, and the investigators concluded that patients who received systematic anti-hypertensive therapy with frequent follow-up fared better than patients who received medical care that was customarily available in the community. But how can the statistically significant finding for all-cause mortality in this trial be reconciled with the negative findings of the seven other study, especially when the mean difference in diastolic blood pressure maintained between the compared groups was among the lowest of any of the eight trials (5 mmHg)? I have proposed two possible explanations: 1) The experimental group was at lower risk at baseline due to ineffective randomization. It is difficult to determine what extent this was a factor because the study population was inadequately described. 2) Those patients in the experimental group received superior general medical care. Due to the design of this study, the effects of general medical care on the one hand, and pharmacologic anti-hypertensive therapy on the other, cannot be distinguished. The authors tried to make a distinction on the basis of cause-specific mortality -- they

noted a 26% reduction in cardiovascular-related deaths in patients receiving "Stepped Care" as opposed to only a 13% reduction in non-cardiovascular-related deaths. There are several problems with their argument. Assuming that their findings with regard to cause-specific mortality are correct, one is still unable to attribute the difference in cardiovascular-related mortality to anti-hypertensive therapy alone. Indeed, the difference in non-cardiovascular deaths argues to the point that subjects in the "Stepped Care" group were healthier at baseline and/or received better general medical care. A separate issue has to do with scientific validity. There was ample opportunity for bias to influence cause-specific mortality despite the fact that all findings were reviewed by a blinded committee. The decisions as to cause of death were made solely on the basis of death certificates. The information on these death certificates was supplied by the physicians who had been providing care for these patients, and the physicians were not blinded as to treatment.

It should be noted that one other study, the VA-Cooperative Group trial, also found a statistically significant difference in cardiovascular-related mortality. This trial also had deficiencies in assigning cause of death. Further methodologic deficiencies of this study will be reviewed shortly in the discussion of all outcome events which follows.

B. All Outcome Events: Mortality and Morbidity

The HDFP study did not attempt to evaluate the efficacy of

anti-hypertensive treatment in the prevention of cardiovascular-related morbidity (i.e. non-fatal events). For the seven remaining trials, the incidence of non-fatal cardiovascular events, major and minor, ranged from a high of 19.6% in the VA-Cooperative Group study to a low of 1% in the VA-NHLBI study. Five of the seven trials (USPH, VA-NHLBI, Chelmsford, Oslo, Japanese) found no difference between treated and untreated patients in the incidence of non-fatal trial end-points.

In the VA-Cooperative Group study, a significant reduction in cardiovascular end points (fatal and non-fatal) was found. This was the first study of "mild hypertension", and of all the studies it showed the greatest difference in morbidity between treated and untreated patients. However, the benefits of treatment were not evenly distributed across the trial population. Indeed, there appeared to be less benefit from treatment in the group of patients with an entry diastolic pressure of 90-104 mmHg (a range which more closely approximates the current concensus of opinion for "mild hypertension"). In addition, this study population was far from being asymptomatic. Well over 50% of the subjects had evidence of target-organ damage at the time of entry -- this undoubtedly contributed to the high incidence of trial end points seen in this study. The fact that patients in the placebo group were allowed to continue in the trial until their diastolic blood pressure exceeded

124 mmHg could have contributed substantially to the difference in cardiovascular end points observed between the compared groups.

The investigators of the Australian study did not find a statistically significant difference between treated and untreated patients in the number of non-fatal end-points. However, they noted that when all outcome events were considered, there was a significant reduction of trial end-points in the treated group. The biggest difference was in the incidence of minor morbid events, and as previously discussed, this finding may be unreliable because there may have been unequal detection of these events due to a failure to blind the physicians.

It is important to note that even in the three studies (VA Cooperative Group study, Australian study, HDFP study) which have claimed to find a statistically significant difference in mortality and/or morbidity between treated and untreated patients, nowhere has it been shown that patients less than 50 years of age benefit from treatment.

CURRENT POLICY AND CONCLUSIONS

Based primarily on the findings of the HDFP study, The Joint National Committee for the Detection, Evaluation, and Treatment of High Blood Pressure issued a policy statement in 1980 on the management of mild hypertension which stated in part:

> "Although reduction in overall mortality has not yet been demonstrated in patients below the age of 50, treatment of these patients reduced the incidence of such hypertensive complications as stroke, congestive

> heart failure, left ventricular hypertrophy, and a progressive increase in blood pressure. It is therefore reasonable to lower blood pressure even in uncomplicated mild hypertension by pharmacologic and non-pharmacologic means." (55)

In a follow-up statement, Dr. Robert Levy, Director of the National Heart, Lung, and Blood Institute, has commented:

> "... some 60 million Americans are at risk due to hypertension and [they] can benefit from therapeutic control. No sustained elevation above 140/90 can be casually dismissed as needing no intervention, and any elevation that is treated should be treated to achieve a specific goal of blood pressure. It has been estimated that between 60,000 to 80,000 premature deaths each year may be averted if these recommendations [of the Joint National Committee] are followed." (56)

Despite these policy statements, I conclude that the evidence available to date does not justify a uniform policy towards the treatment of mild hypertension. The major reason that answers have not been immediately forthcoming has to do with the difficult nature of the problem. Mildly hypertensive patients are at low risk and follow very different courses ultimately experiencing highly variable outcomes. The randomized clinical trials which have been employed to assess the problem of mild hypertension have inherent conflicts. Investigators must ensure that their trials are scientifically valid, feasible, and clinically applicable all at the same time. I contend that a common flaw in the studies performed thusfar is the sacrifice of clinical relevance in favor of scientific validity and feasibility (e.g., type of patients selected for study, types of outcome

events considered, and the consistent omission of possible adverse effects of treatment), and therefore would suggest that future studies be designed and performed with more attention paid to clinical applicability.

Unless we can better define those mildly hypertensive patients who are most likely to benefit from treatment, we may be needlessly committing millions of patients to the inconvenience and expense as well as yet poorly defined risks of life-long anti-hypertensive therapy. Indeed, as physicians we must ask whether a uniform policy of treating all mildly hypertensive patients treats our patients or ourselves.

TABLES

TABLE 1

SUMMARY OF RCT OF MILD HYPERTENSION

Name of Trial	Study Interval	Hypertension Criteria (DBP mmHg)	Follow-up (YRS) Mean (Range)	Number of Patients	Reported Outcome Events‡ % Control	% Treated	Risk-Reduction§ Proportional (%)	Difference (%)
Veterans Admin. (33-35)	1964-69	90-114	3 (1-6)	380	26.9	11.8	-56	-15.1
U.S.P.H. (36)	1965-76	90-114	7 (6-9)	389	46.	29.	-37	-17.0
V.A.-N.H.L.B.I. (37)	1974-76	85-104	1 (1-2)	1012	0.6	0.8	+33	+ 0.2
Chelmsford Group (38)	1966-77	90-110	6 (1-11)	233	13.2	5.4	-59	- 7.8
H.D.F.P. (Group 1) (39-40)	1973-78	90-104	5 (5)	7825	7.4	5.9	-20	- 1.5
Oslo Study (42)	1972-79	95-110*	6 (5-7)	785	9.	6.2	-31	- 2.8
Australian Group (41)	1973-79	95-110	4 (?)	3427	9.8	8.0	-18	- 1.8
Japanese Study (43)	1974-79	90-110†	4 (?)	91	72.3	42.1	-42	-30.2

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*Also used SBP 150-180

†Also used SBP 160-200

‡These are overall outcome rates as reported by investigators. For a listing of the outcome events for each trial, see Appendix A.

§Proportional risk reduction defined as: $\frac{\%\ \text{MORBIDITY}_{\text{control}} - \%\ \text{MORBIDITY}_{\text{treated}}}{\%\ \text{MORBIDITY}_{\text{control}}}$

TABLE 2

SCREENING AND BASELINE STATE DATA

Name of Trial	Number Screened Patients	Number Eligible	Number (%) Admitted	Mean Age (Range)	% MGN	Entry Mean (± s.d.) DBP mmHg	% With End-Organ Damage
Veterans Admin.	?	?	380 (?)	51 (24-75)	100%	104 (?)	58%
U.S.P.H.	1,600	422	389 (24%)	44 (21-55)	80%	99 (?)	0%
V.A.-N.H.L.B.I.	118,157	2,319	1,012 (<1%)	38 (21-50)	81%	93 (?)	0%
Chelmsford Group	?	?	233 (?)	36 (21-50)	36%	99 (5)	0%
H.D.F.P. (Group 1)	159,000	17,476	7,825 (5%)	51 (30-69)	55%	96 (?)	2-5%
Oslo	16,200	2,014	785 (5%)	45 (40-49)	100%	97 (?)	0%
Australian	104,000	?	3,427 (3%)	50 (30-69)	63%	100 (4)	0%
Japanese	?	?	91 (?)	76 (>60)	55%	86 (2)	?

TABLE 3

PERFORMANCE OF MANEUVER†

Name of Trial	Random Allocation of Rx	Active Treatment Fixed vs. Variable	Comparison Treatment	Physician "Blind" to Treatment	Physician "Blind" to Treatment	Criteria for Treating Controls*
Veterans Admin.	Yes	Fixed	Placebo	Yes	Yes	DBP > 124 (3 visits)
U.S.P.H.	Yes	Fixed	Placebo	Yes	Yes	DBP > 130 (3 visits)
V.A.-N.H.L.B.I.	Yes	Variable	Placebo	Yes	Yes	DBP > 120 (2 visits) DBP > 110 (4 visits)
Chelmsford	No	Variable	No Treatment	No	No	DBP > 110 (3 visits)
H.D.F.P.	Yes	Variable	"Referred Care"	No	No	DBP > 115
Oslo	Yes	Variable	No Treatment	No	Yes	SBP $\geq$ 180 DBP $\geq$ 110
Australian	Yes	Variable	Placebo	No	No	DBP > 110
Japanese	No	Variable	Placebo	?	Yes	SBP > 200 DBP > 110

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†For actual treatment protocol see Appendix B.

*DBP = diastolic blood pressure; SBP = systolic blood pressure

TABLE 4

MONITORING OF BLOOD PRESSURE AND STUDY PARTICIPANTS ACCORDING TO TREATMENT ASSIGNMENT

Name of Trial		Target Blood Pressure (mmHg)	Change in SBP (mmHg)	Change in DBP (mmHg)	Time of Observation	Drop-outs (%)*
Veterans Admin.	T	?	-27	-17	4 months	15
	C		- 4	+ 1		15
U.S.P.H.	T	?	-16	-10	4 months	33
	C		0	0		35
V.A.-N.H.L.B.I.	T	< 85	?	-12	8 months	13
	C		?	- 5		16
Chelmsford	T	?	?	?	--	5
	C		?	?		9
H.D.F.P.	T	< 90	?	-10	12 months	9
	C		?	- 5		5
Oslo	T	< 90	-17	-10	16 months	1
	C		0	0		3
Australian	T	< 90	?	-12	12 months	2‡
	C		?	- 7		3
Japanese	T	?	- 9	0	12 months	14
	C		0	- 3		13

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Note: T = treated group; C = control group

*Drop-outs are those patients who were prematurely withdrawn from the trial or otherwise lost to follow-up.

‡Although only ~ 2% of the study population was lost to follow-up, it should be noted that 34% of treated subjects and 37% of control subjects prematurely discontinued their assigned regimen.

TABLE 5

REANALYSIS OF OUTCOME EVENTS: DEATHS

Name of Trial	Deaths, All Causes		% Difference (T-C)	Deaths, Cardiovascular		% Difference (T-C)
	Treated (No.)	Control (No.)		Treated (No.)	Control (No.)	
Veterans Admin.	5.4% (10)	10.8% (21)	-5.4	4.2% (8)	10.0% (19)	-5.8
U.S.P.H.	1% (2)	1% (2)	0	1% (2)	1% (2)	0
V.A.-N.H.L.B.I.	0.4% (2)	0% (0)	+0.4	0.4% (2)	0% (0)	+ .4
Chelmsford	0% (0)	0% (0)	0	0% (0)	0% (0)	0
H.D.F.P.	5.9% (231)	7.4% (291)	-1.5	3.1% (122)	4.2% (165)	-1.1
Oslo	2.5% (10)	2.3% (9)	+0.2	1.8% (7)	1.5% (6)	+0.3
Australian	1.6% (25)	2.0% (35)	-0.4	.5% (8)	1.0% (18)	-0.5
Japanese	18.4% (7)	17.1% (7)	+1.3	7.9% (3)	7.7% (3)	+0.2

TABLE 6

RE-ANALYSIS OF OUTCOME EVENTS: MAJOR MORBIDITY*

Name of Trial	Major Morbidity		
	Treated (No.)	Control (No.)	% Difference (T-C)
Veterans Admin.	4.8% (9)	14.4% (23)	- 9.6
U.S.P.H.	3.1% (6)	3.6% (7)	- 0.5
V.A.-N.H.L.B.I.	0.4% (2)	0.6% (3)	- 0.2
Chelmsford	5.4% (6)	13.2% (16)	- 7.8
H.D.F.P.	?	?	--
Oslo	2.0% (8)	3.2% (12)	- 1.2
Australian	2.4% (41)	2.4% (41)	0
Japanese	2.3% (1)	12.8% (6)	-10.5

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*Major morbidity includes the following non-fatal cardiovascular complications: myocardial infarction, cerebrovascular accidents, and episodes of congestive heart failure.

TABLE 7

RE-ANALYSIS OF OUTCOME EVENTS: MINOR MORBIDITY*

Name of Trial	Minor Morbidity Treated (No.)	Control (No.)	% Difference (T-C)
Veterans Admin.	?	?	--
U.S.P.H.	9.8% (19)	20.9% (41)	-11.1
V.A.-N.H.L.B.I.	Higher in Treated Group†		
Chelmsford	?	?	--
H.D.F.P.	?	?	--
Oslo	1.6% (6)	3.2% (12)	- 1.6
Australian	4.2% (72)	5.4% (92)	- 1.2
Japanese	?	?	--

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*Minor morbidity includes the following non-fatal cardiovascular complications: transient ischemic events, left ventricular hypertrophy, cardiomegaly (determined radiographically), retinopathy, and evidence of renal failure (elevated serum creatinine).

†Actual data was not provided.

TABLE 8

RE-ANALYSIS OF OUTCOME EVENTS:
ADVERSE EFFECTS AND QUALITY OF LIFE

Name of Trial	Treated (No.)	Control (No.)	% Difference (T-C)	Quality of Life Functional Capacity
Veterans Admin.	11.7% (22)	6.3% (10)	+ 5.4%	Not Measured
U.S.P.H.	9.8% (19)	2.0% (4)	+ 7.8%	Not Measured
V.A.-N.H.L.B.I.	~300% (1479)	~140% (701)	+ 160%	Not Measured
Chelmsford		Not Measured		Not Measured
H.D.F.P.		Not Measured		Not Measured
Oslo		Measured but Data Not Provided		Not Measured
Australian		Not Measured		Not Measured
Japanese		Not Measured		Not Measured

BIBLIOGRAPHY

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1. Paton, W.D.M. and Zamais, E.J. Br. J. Pharmacol. 4: 381 (1949).

2. Keith, N.M. and Wagener, H.P. Am. J. Med. Sci. 197: 332, (1939).

3. McMichael, J. The management of hypertension. Br. Med. J. 1: 933 (1952).

4. Dustan, H.P., et al. The effectiveness of long-term treatment of malignant hypertension. Circulation 18: 644-651 (Oct. 1958).

5. Harrington, M., Kincaid-Smith, P., and McMichael, J. Results of treatment in malignant hypertension. Br. Med. J. 2: 969-989 (Nov. 14, 1959).

6. Sokolow, M. and Perloff, D. Five-year survival of consecutive patients with malignant hypertension treated with antihypertensive agents. Am. J. Cardiol. 6: 858-863 (Nov. 1960).

7. Mohler, E.R. and Freis, E.D. Five-year survival of patients with malignant hypertension treated with antihypertensive agents. Am. Heart J. 60: 329-335 (Sept. 1960).

8. Perry, H.M. Jr. and Schroeder, H.A. The effect of treatment on mortality rates in severe hypertension. A comparison of medical and surgical regimens. Arch. Int. Med. 102: 418-425 (Sept. 1958).

9. Björk, S., et al. The effect of active drug treatment in severe hypertensive disease. Acta. Med. Scand. 169: 673-689 (June, 1961).

10. Leishman, A.W.D. Hypertension--Treated and untreated--A study of 400 cases. Br. Med. J. 1: 1361-1368 (May 30, 1959).

11. Perera, G.A. Antihypertensive drug versus symptomatic treatment in primary hypertension: Effect on survival. J.A.M.A. 173: 11-13 (May 7, 1960).

12. Veterans Administration Cooperative Study Group on Antihypertensive Agents. Effects of treatment on morbidity in hypertension: Results in patients with diastolic blood pressure averaging 115 through 129 mmHg. J.A.M.A. 202: 1028-1034 (1967).

13. Hamilton, M., in Gross, F. (ed.). Antihypertensive Therapy: Principles and Practice, an International Symposium. New York: Springer-Verlag New York, Inc., pp. 196-211, 1966.

14. Woiff, F.W. and Lindeman, R.D. Effects of treatment in hypertension: Results of a controlled study. J. Chron. Dis. 19: 227-240 (March, 1966).

15. Shurtleff, D. Some characteristics related to the incidence of cardiovascular disease and death: Framingham study, 18-year follow-up, in The Framingham Study: An Epidemiological Investigation of Cardiovascular Disease, publication No. (NIH) 74-599. Washington, DC, US Dept. of Health, Education, and Welfare, February, 1974, section 30.

16. US Dept. of Health, Education, and Welfare: Blood Pressure of Persons 18-74 Years, United States, 1971-72, series 11, No. 150. National Health Survey, National Center for Health Statistics, 1975.

17. Feinstein, A.R. The epidemiologic trohoc, the ablative risk ratio, and retrospective research in Clinical Biostatistics. St. Louis, Missouri. The C.V. Mosby Co., pp. 197-213, 1977.

18. Sackett, D.L. Bias in analytical research. J. Chron. Dis. 32: 51 (1979).

19. Horwitz, R.I. and Feintein, A.R. The application of therapeutic tiral principles to improve the design of epidemiologic research--A case-controlled study suggesting that anticoagulants reduce mortality in patients with myocardial infarction. J. Chron. Dis. 34: 575 (1981).

20. Feinstein, A.R. The purposes of prognostic stratification in Clinical Biostatistics. St. Louis, Missouri. The C.V. Mosby Co., pp. 414-429, 1977.

21. Feinstein, A.R. The scientific and clinical tribulations of randomized clinical trials. Clin. Res. 26: 241 (1978).

22. Chalmers, T.C. The method for assessing the quality of randomized clinical trials. Con. Clin. Trials 2: 31 (1981).

23. Peto, R. and Pike, M.C. Design and analysis of randomized clinical trials requiring prolonged observation of each patient. Br. J. Cancer 34: 585 (1976).

24. Carleton, R.A., Sanders, C.A., and Burack, W.R. Heparin administration after acute myocardial infarction. N. Engl. J. Med. 263: 1002 (1960).

25. Feinstein, A.R. Credulous idolatry and randomized allocation in Clinical Biostatistics. St. Louis, Missouri. The C.V. Mosby Co., pp. 105-121, 1977.

26. Feinstein, A.R. The difficulties of pharmaceutical surveillance in Clinical Biostatistics. St. Louis, Missouri. The C.V. Mosby Co., pp. 271-286, 1977.

27. Chalmers, T.C. In defense of the VA randomized control trial of coronary artery surgery. Clin. Res. 26: 230 (1978).

28. Proudfit, W.L. Criticisms of the VA randomized study of coronary bypass surgery. Clin. Res. 26: 236 (1978).

29. Schor, S. The university group diabetes program. A statistician looks at the mortality results. J.A.M.A. 217: 1671 (1971).

30. Alderman, M.H. Mild hypertension--New light on an old clinical controversy. Am. J. Med. 69: 653 (1980).

31. Alderman, M.H. and Madhaven, S. The potential effect of blood pressure reduction on cardiovascular disease--A cutionary note. Arch. Int. Med. 141: 1583 (1981).

32. Feinstein, A.R. Random sampling and medical reality in Clinical Biostatistics. St. Louis, Missouri. The C.V. Mosby Co., pp 154-168, 1977.

33. Freis, E.D., in Gross, F. (ed.). Antihypertensive Therapy: Principles and Practice, an International Symposium. New York: Springer-Verlag New York, Inc., pp. 345-354, 1966.

34. Veterans Administration Cooperative Study Group on Antihypertensive Agents. Effects of treatment on morbidity in hypertension: II results in patients with diastolic blood pressure averaging 90 through 114 mmHg. J.A.M.A. 213: 1143-1152 (1970).

35. Veterans Administration Cooperative Study Group on Antihypertension Agents. Effects of treatment on morbidity in hypertension: III influence of age, diastolic pressure, and prior cardiovascular disease; further analysis of side effects. Circulation 45: 991-1004 (1972).

36. US Public Health Service Hospitals Cooperative Study Group (Smith, W.M.). Treatment of mild hypertension: Results of a ten-year intervention trial. Circ. Res. 40(suppl. 1): 98: 105 (1977).

37. Veterans Administration--National Heart, Lung, and Blood Institute Study Group for Cooperative Studies of Antihypertensive Therapy: Mild hypertension (Perry, H.M.). Treatment of mild hypertension: Preliminary results of a two-year feasibility trial. Circ. Res. 40(suppl. 1): 180-187 (1977).

38. Johnson, H.B. and Pearce, V.R. Treatment of mild hypertension. An attempted controlled therapeutic trial. J. Chron. Dis. 31; 513 (1978).

39. Hypertension Detection and Follow-up Program Cooperative Group. Five-year findings of the hypertension detection and follow-up program. Reduction in mortality of persons with high blood pressure, including mild hypertension. J.A.M.A. 242: 2562-2571 (1979).

40. Hypertension Detection and Follow-up Program Cooperative Group. Five-year findings of the hypertension detection and follow-up program. Mortality by race, sex, and age. J.A.M.A. 242: 2572-2577 (1979).

41. Australian National Blood Pressure Management Committee. The Australian therapeutic trial in mild hypertension. Lancet i: 1261-1267 (1980).

42. Helgeland, A. Treatment of mild hypertension: A five-year controlled drug trial. The Oslo study. Am. J. Med. 69: 725-732 (1980).

43. Kuramato, K. and Matsushita, S. Prospective study on the treatment of mild hypertension in the elderly. Jpn Heart J 23: 75 (1981).

44. M.R.C. Working Party on Mild to Moderate Hypertension. Randomised controlled trial of treatment of mild hypertension: design and pilot trial. Br. Med. J. ii: 48 (1977).

45. Amery, A., Berthaux, P., Birkenhager, W., et al. European working party on high blood pressure in elderly. Antihypertensive therapy in patients above age 60. Acta. Cardiol. 33: 113-134 (1978).

46. Paul, O. Risks of mild hypertension--ten-year report, Br. Heart J. 33: 116 (1971).

47. Report of a cooperative randomized controll trial: Control of mildly raised blood pressure. Br. Med. J. 3: 434 (1973).

48. Guidelines for the detection, diagnosis, and mangement of hypertensive populations, in Wright, I.S., Fredrickson, D.T. (eds.): Cardiovascular Diseases: Guidelines for Prevention and Care, Inter-Society Commission for Heart Disease Resources, Hypertension Study Group. US Government Printing Office, pp. 186-197, 1974.

49. The Hypertension Detection and Follow-up Program, Hypertension Detection and Follow-up Program Cooperative Group. Prev. Med. 5: 207-215 (1976).

50. Therapeutic control of blood pressure after one year in the Hypertension Detection and Follow-up Program, Hypertension Detection and Follow-up Program Cooperative Group. Prev. Med. 8: 2-13 (1979).

51. Abernethy, J.D. The Australian National Blood Pressure Study. Med. J. Aust. i: 821 (1974).

52. Leren, P., Askevold, E.M., Foss, O.P., et al. The Oslo Study. Cardiovascular disease in middle-aged and young Oslo men. Acta. Med. Scand. (suppl. 588): 6 (1975).

53. Stamler, J. Reduction in mortality among persons with mild hypertension. Presentation at a meeting of the American College of Cardiology, Houston, 1980.

54. W.H.O./I.S.H. Mild Hypertension Liaison Committee. Trials of the treatment of mild hypertension--an interim report. Lancet i: 149 (1982).

55. Joint National Committee Report on the Detection, Evaluation, and Treatment of High Blood Pressure, Iqbal Krishan (Chairman). Arch. Int. Med. 140: 1280-1285 (1980).

56. Levy, R.I. Hypertension control--the challenge is now. Chest 76: 803 (1980).

57. Relman, A.S. Mild hypertension--no more benign neglect. N. Engl. J. Med. 302: 293 (1981).

58. Smith, W.M. Treatment of mild hypertension in drug therapeutics. Edited by K.C. Melmon. New York, New York. Elsevier North Holland, Inc., pp. 3-15, 1981.

59. Stamler, J., Farinaro, E., and Mojonnier, L. Prevention and control of hypertension by nutritional hygienic means. J.A.M.A. 243: 1819 (1980).

60. Moses, C. Drug treatment of mild hypertension--adverse consequences. Ann. NY Acad. Sci. 304: 84 (1978).

61. Haristen, P.D. Drug Interactions. Second Edition by Lea and Febriger. Philadelphia, PA, 1973.

62. Report of the Medical Research Council Working Party on Mild Hypertension: Adverse reactions to bendroflumethiazide and propranolol for the treatment of mild hypertension. Lancet i: 539 (1981).

63. Oliver, M.F. Risks of correcting the risks of coronary disease and stroke with drugs. N. Engl. J. Med. 306: 297 (1982).

64. Personal communication, September 1981.

65. Personal communication, September 1981.

66. Leren, P., Foss, P.O., Helgeland, A., Hjermann, I., Holme, I., Lund-Larson, P.G. Effect of propranolol and prazosin on blood lipids: The Oslo study. Lancet ii: 4-6 (1980).

67. Carlson, L.A., Böttiger, L.E., Ahfeldt, P-E. Risk factors for myocardial infarction in the Stocholm prospective study: 14-year follow-up focussing on the role of plasmas triglycerides and cholesterol. Acta. Med. Scand. 206: 351-360 (1979).

68. Miller, G.J. and Miller, N.E. Plasma-high-density-lipoprotein concentration and development of ischaemic heart-disease. Lancet i: 16-19 (1975).

APPENDICES

APPENDIX A

COMPARISON OF EVENTS CONSTITUTING END POINTS*

Name of Trial	Major Outcome Events	Minor Outcome Events
	Class A Events (require termination):	Class B Events (do not require termination):
1. Veterans Admin.	1. Papilledema 2. Cerebral or subarachnoid hemorrhage 3. Dissecting aortic aneurysm 4. CHF (uncontrolled) 5. ↑ BUN 6. Hypertensive endephalopathy	1. MI 2. CHF (controlled) 3. Arrhythmia 4. Heart Block 5. CVH 6. Pulmonary embolism 7. CVA 8. TIA 9. ↑ BUN 10. Proteinuria 11. Hematoma 12. Vascular insufficiency
2. U.S.P.H.	1. Death cardiovascular sudden death 2. MI 3. CVA	1. Vascular insufficiency, coronary cerebral, renal 2. CHF 3. Encephalopathy
3. V.A.-N.H.L.B.I.	1. MI 2. Sudden death	Not Measured
4. Chelmsford Group	1. MI 2. CVA 3. CHF	Not Measured
5. H.D.F.P.	1. Death (all causes) 2. Death by cause a. cardiovascular b. non-cardiovascular	Not Measured
6. Oslo Study	1. Deaths a. cardiovascular b. other	Major Cardiovascular Disease: MI, angina, CVA, CHF, CVH
7. Australian Group	1. Deaths a. cardiovascular b. other	Non-Fatal Events: CVA, TIA, MI, CHF, retinopathy, renal failure
8. Japanese Study	1. Deaths a. cardiovascular b. other	Cardiovascular Complications: MI, CVA, CHF, elevated BP

*As defined by trials

APPENDIX B

STUDY PROTOCOL

Name of Trial	Active Regimen	Compared Regimen	Ancillary Measures
Veterans Admin.	1. 50 mg hydrochlorothiazide BID .1 mg reserpine BID Hydralazine 25 mg TID	Placebo	Not stated
U.S.P.H.	1. 500 mg chlorothiazide BID 100 mg rauwolfia serpentina BID	Placebo	Not stated
V.A.-N.H.L.B.I.	1. 50 mg chlorothiazide BID 2. 100 mg chlorothiazide BID 3. 100 mg chlorothiazide BID .25 mg reserpine BID	Placebo	Not stated
Chelmsford	1. Thiazide diuretic 2. Thiazide plus methyldopa or chloidine	No treatment	Not stated
	Stepped Care	Referred Care	
H.D.F.P.	1. No treatment when BP < 90 mmHg 2. Diuretic 3. Diuretic plus reserpine or aldomet 4. Diuretic, reserpine, or aldomet and hydralzine	Patients were referred to their usual source for medical care.	For "Stepped Care" group only.
Oslo	1. 50 mg hydrochlorothiazide 2. 50 mg hydrochlorothiazide 250-500 mg methyldopa	No Treatment	Similar advice provided to both groups.
Australian	1. No treatment when BP < 90 mmHg 2. Diuretic 3. Diuretic plus aldomet or propranolol 4. Diuretic, aldomet, or propranolol and hydralazine	Placebo	Similar advice provided to both groups.
Japanese	1. Diuretic 2. Diuretic plus methyldopa, reserpine, or hydralazine	Placebo	Not Stated

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